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CLINIC OF DR. THOMAS McCRAE

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## THE EARLY DIAGNOSIS OF EMPYEMA IN LOBAR PNEUMONIA

THE occurrence of empyema in lobar pneumonia is something which we have to expect in a certain number of cases, but the proportions may vary greatly from year to year. During this year you have seen several cases and we have discussed various features concerning its recognition and treatment. In this clinic I wish to go over the experience of the year with especial reference to the early diagnosis. There are certain features of the problem of empyema in lobar pneumonia which may be discussed.

1. Frequency.—This varies from year to year and of the factors which govern this we know very little. In large collections of cases the proportion of empyema is usually between 2 and 3 per cent. Thus Norris and Farley in the Osler System report a collected series of 13,550 cases of lobar pneumonia with 2.2 per cent. of empyema. In my service for the last three years the percentages were 7, 4.8, and 7.7, and this year it is 9.5 per cent. There seem to be "empyema years" when the percentage is high, but even with this there may be curious differences in hospitals which are near each other. For example, the occurrence of empyema in lobar pneumonia in the Jefferson and Pennsylvania Hospitals may show very different figures in the same year. There is some relationship with the type of pneumonia, as Type I has the largest incidence in some large series of cases,



with Type IV coming second, but this does not explain the high figures we have had in three of the last four years.

2. Is Empyema in Lobar Pneumonia a Complication or Sequel?—You will find that there is a difference of opinion as to the answer to this question. It is evidently important that we should endeavor to settle this point. Let us discuss some of the reasons for this. We may say that in general the profession has no great reason to be proud of the average way in which empyema is handled. Too often it is unrecognized for a period which means that important time is lost to the detriment of the patient. He has a right to ask of the physician that his empyema be recognized as early as possible so that proper treatment can be begun at the best time. The surgeon has the right to ask of the physician that he be called to see the patient at as early a stage of the empyema as possible, so that he can plan the best treatment. From the surgeon the patient has the right to ask the most skilful management, so that he has the best chance for recovery in the shortest possible time and with the least permanent disability.

The view which I hold very strongly is that in the vast majority of cases empyema with lobar pneumonia is a *complication* and not a sequel. In other words, the empyema is present before the pneumonia has terminated. I grant that it may not be recognized until the pneumonia is over, but this does not mean that it was not present. The lesson is obvious, and we should have empyema in mind as a possibility in every patient with lobar pneumonia from the onset of the disease. I do not know what is the earliest time at which empyema may be present; you will remember that last year you saw a patient in whom it was recognized and proved by aspiration on the third day of the attack of pneumonia.

Empyema does occur as a sequel, but this is very rare in my opinion and does not reduce the emphasis which should be laid on its occurrence as a complication.

Many things in medicine are recognized only if you look for them. Always have empyema in mind as a possibility in every patient with pneumonia, but remember that fluid in the

pleural cavity in pneumonia is not always purulent. It is possible that small amounts of serous fluid are not uncommon. Large serous effusions are rare, but do occur and, as a rule, are extremely serious. What is said here as to the means of recognition of the presence of pleural fluid in lobar pneumonia applies to both serous and purulent effusions.

There were two patients in whom there was no question of the occurrence of empyema during the course of the pneumonia. Some of you saw them in the ward and also in the autopsy room.

*Case I.*—The patient, a colored male, aged twenty-eight years, was admitted on March 6th with a history of a sudden onset of dyspnea on March 2d. This was followed by a severe chill, a racking cough with blood-stained sputum, fever, and frequent vomiting. He presented a typical picture of severe pneumonia with involvement of the middle and lower right lobes. His condition was serious from the time of admission and the grave outlook owing to his general condition was supported by the fact that his maximum leukocyte count was 9000. The cultures showed Type IV pneumococcus. On the last day there were signs of involvement of the lower left lobe and of fluid in the left pleural cavity, but the patient's condition was so serious that he was not disturbed by tapping. He died on March 10th, the ninth day of the disease.

*Autopsy.*—This showed consolidation of the middle and lower lobes on the right side and an early stage of consolidation in the left lower lobe. Over both lungs there was a thick exudate, and in the left pleural cavity about 200 c.c. of thin purulent fluid.

*Remarks.*—By the ninth day of the attack of pneumonia there was an empyema on the left side. So far as we observed the signs in the left thorax were present not more than thirty-six hours before death. It is possible that with the involvement of the right side—the original site—there had been an empyema on the left side before the pneumonic involvement of the lower left lobe. This may occur although it is not common. In any event the empyema was present before the pneumonia showed any signs of resolution.

*Case II.*—The patient, a colored male, aged forty years, was admitted on March 16th, with a history that on March 9th he had a severe chill with thoracic pain and cough. However, these did not make him give up work, which he continued until March 12th. He then went to bed, where he remained until admission. He was desperately ill when brought to the hospital. There were extensive signs over the left thorax with marked dullness over the lower part with much decreased vocal fremitus. The breath-sounds were much diminished over the lower left thorax. The cardiac impulse could neither be seen or felt, and the heart-sounds were not heard. The signs suggested a pericarditis with effusion and a pleural effusion on the left side, both probably purulent. The leukocytes were 64,000. The pulse could not be

counted accurately and the respirations were 52. His condition was hopeless and there was no object in tapping the pericardium or pleura. He died five hours after admission.

*Autopsy.*—The left lung was covered with a thick purulent exudate, and the left pleural cavity contained a considerable amount of greenish-yellow pus. The lower left lobe was consolidated and the left upper lobe was compressed. The pericardium showed an acute purulent pericarditis. The cultures showed Type IV pneumococcus.

*Remarks.*—It is difficult to state on which day of the disease this patient died. If the onset was on March 9th it was on the eighth day; if March 12th was the actual day of onset, death occurred on the fifth day. In any event he had a well-marked empyema before the pneumonia had terminated.

3. **Diagnosis of Empyema in Lobar Pneumonia.**—First let us remember that the problem is a difficult one in comparison with the recognition of empyema not due to lobar pneumonia, but the difficulties should stimulate us to be the more alert to overcome them. There are several factors which may contribute to the difficulty of diagnosis. One is the condition of the patient. If the attack is severe and the patient very ill, we properly disturb him as little as possible and may not be able to make a complete examination. This does not make a great difference, as in all probability we would not be able to do anything in the way of treatment until the outcome of the pneumonia was decided. A second point is the difficulty of the problem of the physical signs. The lung is consolidated and the presence of a small amount of fluid, usually at the base, may be difficult to prove. Those who do not seem to be able to recognize fluid in the pleura by their own senses but must have an x-ray study will be helpless here, because the x-ray plate is not likely to show any difference between the shadow cast by fluid and that by a consolidated lung. So you need not expect to throw the burden of diagnosis on the radiologist. You must carry it yourself. Please remember that we are discussing the *early* diagnosis of empyema particularly, that is, while it is a complication of an active pneumonia.

There is one point to keep well in mind, and that is the usual physical conditions which exist when empyema occurs with an air-containing lung. In this event the lung can collapse and occupy less space, but when the lung is consolidated this cannot

occur and the empyema fluid has relatively small space to occupy. If the upper lobe is not involved, it may collapse to some extent and give more space. It is evident that fluid forming about a consolidated lung is likely to extend upward to an extent quite out of keeping with our ideas of empyema without consolidation. The lower part of the lung is often adherent to the diaphragm, which further lessens the available space for the fluid. Also the layer of fluid is likely to be thin in the early stages, an important point in diagnosis, to which we shall return.

Let us discuss the various means of diagnosis and see which of them are useful. Let me repeat that we are concerned to-day with the early recognition of empyema while the pneumonia is still in progress.

(a) General Features.—These are not likely to help us, as the patient has fever, toxemia, dyspnea, and thoracic pain from the pneumonia. No one of them is going to be greatly increased by the occurrence of empyema.

(b) Cough.—There may be information gained from this which may rouse our suspicions of empyema. There may be a series of short hacking coughs with little or perhaps no expectoration—not diagnostic, but suggestive.

(c) Leukocytes.—There is no information from their number.

(d) Inspection.—The affected side shows diminished expansion from the pneumonia and so gives us no aid.

(e) Palpation.—This may be of considerable aid if the patient's voice sets up vibrations strong enough to carry. The decrease in the vocal fremitus is of great value and, as we try to observe it over a small area, the use of the ulnar side of the hand is valuable, or a finger may be laid on to observe sharply marked changes. In some cases the vocal fremitus is *diminished but not absent*. If the layer of fluid is thin the vibrations are not stopped entirely. In some cases vocal fremitus may be felt, but diminished, over an area where there is flatness and marked resistance. It is the decrease which is significant, and this requires careful daily observation. The finding of a local area of tenderness is of value if it occurs.

(f) **Percussion.**—You know my views on percussion—that it is the method of examination which is usually performed least skilfully and the one which requires the longest training in which to become efficient. I refer not only to the production of the note but also to the estimation of the sense of resistance. The latter, in my opinion, is the most important single thing in the diagnosis of fluid in the pleural cavity. To obtain help from percussion in this problem you must observe the note each day and keep in mind the character of the preceding day's findings. With a very sick patient we do not wish to turn the patient or sit him up, but the note in the lower axilla is usually sufficient. With this must go an accurate sensing of the amount of resistance. Only steady work and faithful observation can give you this, but it is well worth the effort.

(g) **Auscultation.**—Here again the comparison of daily observations is important. The breath-sounds become more distant, but rarely disappear entirely in early stages of empyema. If there has been a friction-rub it disappears. Râles may still be heard and with about as much loudness as before. If râles are present about which there is doubt as to their lung or pleural origin, this may deceive if they are regarded as pleural. Changes in the voice-sounds are important. Over fluid which is not very thick they are heard loudly and with a peculiar nasal quality which is not to be recognized by any description, but only by hearing it. The voice vibrations are exaggerated by the consolidated lung and often come through a layer of fluid with surprising loudness. Do not exclude the presence of fluid because of loud voice-sounds. In some cases the change in the voice-sounds is very marked over areas not more than an inch apart.

In the majority of cases a thorough study of the physical signs should make one suspicious of fluid and in many cases practically certain of it. If there is doubt and in all cases for positive confirmation one should use the exploring needle.

(h) **Exploring Needle.**—This can be introduced into the lower axilla with very little disturbance of the patient. It is well to use a local anesthetic. The fact that the layer of fluid at this

early stage of an empyema is very thin should be kept in mind and the point of the needle inserted just deep enough to go through the pleura. The sensation given by the needle passing into the consolidated lung is usually definite and if this occurs it should be withdrawn very slowly. Thin layers of fluid are often missed because this point is forgotten. As a rule it is well to introduce the needle into the area where the greatest resistance is found, but there should be no hesitation in needling in several areas if the first taps are negative.

(2) *x-Ray*.—This cannot be expected to give us any aid, certainly not in the majority of cases.

You may ask what advantage there is in making the diagnosis of empyema during the course of the attack of pneumonia. There are several points concerned. It should always be a source of satisfaction to know the exact condition of your patient, especially as regards the presence of a complication. You know as early as is possible of the presence of a condition with which you have to deal. You give yourself, if you are to treat the empyema, the chance of managing it in the best possible way or your surgical colleague the same opportunity. You also save yourself much embarrassment by not having to explain to the surgeon why you were so slow in diagnosing the empyema if it is two or three weeks after the attack of pneumonia when you call him. Last and most important of all, you do the best for the patient. This may be in one of several ways. You may be able to save the necessity for operation by prompt tapping, to which we return later. You may shorten the duration of the illness materially by prompt operation if this is required. Every day that a pneumococcus empyema goes unrecognized the risks to the patient are increased. He may be steadily losing ground or some other complication, such as pericarditis, may supervene. There is also the risk of changes occurring in the pleura resulting in extensive fibrosis and preventing proper expansion of the lung. Thus in one case some years ago in which the empyema was drained on the tenth day of the pneumonia, the patient died on the twenty-fourth day from streptococcus septicemia. At autopsy the pleura showed marked thickening.

With this there may be marked fibroid change in the lung, as was found in a patient who died about three weeks after the onset of the pneumonia. The empyema had been drained, but there was marked collapse of the lung, thickened pleura, and marked fibrosis.

Of particular interest is the question as to how often we can cut short the progress of an empyema by early tapping. Stress is laid on the word *early*, but you have the chance to try this only if you are alert and recognize it in time. It is often stated that in children an empyema may be managed by tapping only, but this may occur in adults as well, and we usually have one or two such cases each year. You saw this patient, the history of whom is as follows:

Case III.—Lobar Pneumonia with Empyema Proved on the Ninth Day of the Illness. Recovery After Tapping.—The patient, a colored man, aged forty-three years, was admitted on January 29th, the first day of his illness. His past history gave nothing of importance. On January 28th there was a heavy snow storm and he joined one of the gangs at work cleaning the streets, working from 11 P. M. on January 28th until noon on January 29th. He then had a heavy meal and soon after this felt a severe pain in the lower left thorax which radiated to the region of the umbilicus. After this he had a severe shaking chill and about the same time began to cough. He came to the hospital about 3 P. M. on January 29th. His temperature was 104.4° F. and the leukocytes 12,000 on admission.

The patient had dyspnea, and the signs were of involvement of the lower left lobe. On January 30th there was a well-marked friction-rub heard over the lower left lobe. The breath-sounds became tubular and were accompanied by fine crackling râles regarded as pulmonary. The general signs of toxemia became more marked. The physical signs over the lower left lobe remained much the same and the friction-rub was much less distinct and it had disappeared on February 5th. The breath-sounds were not heard as loudly over the lower back and axilla, but were definitely tubular with a suggestion of an amphoric quality. The voice-sounds came through with a nasal quality. A few distant râles were heard. On February 6th (the ninth day of the disease) the signs were much the same, but the resistance seemed distinctly increased and fluid was suspected. The patient was severely ill.

Remarks.—The signs suggested particularly one of two things: (1) The presence of fluid in the pleura, or (2) a marked amount of fibrinous exudate. If fluid was present it had been there for two days only, as the friction-rub had been well heard on February 5th and it was not in large amount. The increase in resistance and the change in the breath- and voice-sounds were both in favor of fluid. The use of an exploring needle was definitely indicated.

On February 6th a needle was introduced in the lower left axilla and 50 c.c. of thin purulent fluid were withdrawn. The smears showed many pus-cells but no organisms. The cultures made from the pleural fluid did not give any growth. The blood-cultures were negative throughout. Following this the fever continued and fell by crisis on February 10th, which corresponded to the fourteenth day of the disease. At no time was there any evidence of pneumonic involvement of any part of the lung other than the lower left lobe. After the drop in temperature the consolidated lung cleared rapidly. On December 12th the dulness was much diminished, there were a certain number of medium lung râles, but there was no return of the friction-rub. On February 14th some tympany was obtained in the left axilla and also in the left back. The vocal fremitus came through well, the breath-sounds were fairly well heard and were practically normal. By February 17th the condition had cleared entirely and it was not possible to make out any evidence of disease.

In this patient the empyema was present in all probability on February 5th which was the eighth day of the disease, and was definitely proved by removal of pleural fluid on February 6th which was the ninth day of the disease.

There are several points which suggest themselves for discussion. How often does a condition such as this occur with lobar pneumonia and clear spontaneously? No one can answer this, but my own feeling is that it probably occurs much more frequently than is generally recognized. There is no question of the fact that these cases occur and it is certainly to the patient's advantage to have the tapping done, because in some of them this may turn the scale and enable the individual to take care of the pleural infection without drainage.

*The Significance of the Absence of Organisms.*—We can only theorize regarding this, and it might be suggested that we are dealing here with a condition in which the immunity was good, in the pleura at any rate, and that the protective substances were able to overcome the infection. You will note that no organisms were found in the purulent fluid and that there was no growth in the cultures. Naturally this offers the best chance for such a condition being overcome by the patient himself without the need of operation.

It is only by the constant study of all patients that we can hope to have any idea as to how frequently a condition such as this occurs. We usually have about two patients of this kind in the clinic each year. As a rule, they clear up rapidly. In this patient, so far as we can tell, the pleural condition was improved before the pneumonic process had come to an end.

It must not be supposed, however, that the diagnosis of empyema is always made easily. In the following case there was considerable difficulty before we were certain of it.



**Case IV.**—The patient, a colored man, aged twenty-seven years, was admitted on April 17th, complaining of pain in the left thorax. He gave a history that on April 16th, early in the morning, he was taken with very severe pain in the chest, followed later by cough but without any chill. On admission he showed involvement of the lower left lobe with typical signs of pneumonia. On April 19th the dulness at the base was very marked and the breath-sounds were less distinct; crackling râles were heard, medium to coarse in quality. The vocal fremitus was present, but decidedly diminished. A needle was introduced, but fluid was not obtained. The signs continued much the same at the base until April 26th, when the needle was used again in several places, with negative results. There were now signs of consolidation in the upper left lobe. On April 28th the signs suggesting fluid at the base were more marked, but aspiration was negative. We felt that fluid was present, but could not prove it. On April 30th (the fifteenth day of the disease) exploration in the seventh interspace was negative, but pus was obtained in the tenth interspace in the back. The fever continued very steady throughout, partly due to extension of the pneumonic process in the upper left lobe.

*Remarks.*—In this patient we were suspicious of fluid on the fourth day of the disease, but did not find it until the fifteenth day, despite numerous punctures. Was it there all the time and did we fail to find it? I do not know. We had inserted the needle close to the area where we finally found pus. The continuance of fever at the same high level throughout was probably due to the extension of the pneumonic process. Drainage was done on the sixteenth day and the temperature rapidly fell to normal.

There is one condition which will give you the greatest difficulty in diagnosis, and that is the occurrence of an unusually large amount of fibrinous exudate over the lung. It is evident that this will alter the physical signs much as would a thin layer of fluid. One point which may be of aid in the diagnosis is that a fibrinous exudate reduces the voice vibrations which we feel more than those which we hear as sounds. The vocal fremitus may be definitely decreased while the voice-sounds come through clearly. They do not usually show the nasal quality which is often characteristic in empyema. Naturally empyema may occur in a patient with a profuse fibrinous exudate. As a rule, the decision has to be made by the needle and there should be no hesitation in using it.

The points which are emphasized are as follows:

1. Think of empyema in lobar pneumonia as a complication of the disease which may be present early in the course and not as a sequel.

2. Do not wait for the persistence of fever for two or three weeks after the pneumonic process is over to suggest the possibility of empyema. Do not give the surgeon the chance to think—he may be too polite to say it—that there has been a lack of diagnostic ability when an empyema is unrecognized for weeks.

3. Study the physical signs carefully with empyema in mind, and if you diagnose it early try if tapping may prevent the need of drainage.

4. Do not be afraid to use the exploring needle.



## CONTRIBUTION BY DR. DAVID RIESMAN

CARDIOLOGIC SEMINAR LECTURE, DELIVERED BEFORE THE PHILADELPHIA COUNTY MEDICAL SOCIETY AND BEFORE THE NEW UTRECHT MEDICAL SOCIETY OF BROOKLYN

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### DISEASE OF THE CORONARY ARTERIES

FROM the days of Morgagni and of John Hunter until comparatively recent times disease of the coronary arteries remained a casual autopsy finding of little practical interest. Lately, however, it has assumed an extraordinary clinical importance. The attention it is receiving is altogether deserved, for coronary disease strikes at life and at comfort in living as no other human ailment. It is responsible for a large number of tragically sudden deaths, although in such circumstances a diagnosis of coronary disease is not often made.

Our knowledge of the affection is still incomplete. We have not yet penetrated into the essence of cardiac pain which is the outstanding symptom of coronary disease, nor do we understand fully the physiology of the coronary circulation, despite much research by many investigators. Gross in his splendid monograph, and Eiman, as well as Oberhelman and Le Count<sup>1</sup> and F. M. Smith<sup>2</sup> have emphasized the important fact that the coronary arteries are not really end-arteries in the Cohnheimian sense, but have many actual and potential anastomoses.<sup>3</sup>

The coronary arteries are branches of the aorta and the blood they carry returns to the heart by way of the coronary veins and sinuses. They possess an unusually rich nerve supply,

<sup>1</sup> Jour. Amer. Med. Assoc., April 26, 1924.

<sup>2</sup> Amer. Jour. Med. Sci., July, 1918, October, 1923.

<sup>3</sup> See also Anrep, Phys. Rev., vi, 4, October, 1926, p. 596.

both vasoconstrictors coming from the vagus and vasodilator, of sympathetic origin. The time when the coronary artery is filled is a question much discussed and investigated, and though a definite answer is still wanting, the preponderating opinion is in favor of their filling during the systole of the heart. Smith, Miller, and Graber<sup>1</sup> hold that the coronary flow to a large extent depends on the height of the diastolic pressure. It is a pathologic peculiarity not yet explained that the coronary arteries may be diseased while all other parts of the vascular system are unaffected.

We may classify coronary disease from the anatomical point of view as follows:

- (a) Sclerosis—coronary endarteritis.
- (b) Thrombosis with or without complete occlusion.
- (c) Embolism.

Very extensive sclerosis may exist without clinical symptoms during life—this is one of the mysteries of medicine. Whatever its ultimate significance, it is proof that the heart possesses large factors of safety. The sclerotic process may affect the coronary opening or it may appear in the form of scattered patches or as a diffuse endarteritis with or without calcification. An interesting fact has been brought out by Wolkoff.<sup>2</sup> He found that the thickening of the intima of the coronary artery surpasses that found in other arteries at the same age.

Clinical symptoms may be produced in one of three ways:

1. By sudden stoppage of the flow through thrombosis or embolism.
2. By progressive endarteritis narrowing the lumen.
3. By spasmodic closure.

Whatever the method, the result is either a sudden or a gradual ischemia and suboxidation (histanoxia<sup>3</sup>) in the supplied territory.

**Causes of Coronary Disease.**—The causes of coronary disease, as of angina pectoris, are as obscure as those of disease

<sup>1</sup> Arch. of Internal Medicine, July 15, 1926.

<sup>2</sup> Virchow Arch., 241, 42, 1923.

<sup>3</sup> A word I have proposed for local or tissue anoxemia.

in other arteries of the body, as indeed of all degenerative processes. From a clinical point of view the following conditions possess more or less significance:

1. *Cardiovascular heredity*—by that I mean the inheritance in families of tissues which the Germans call *minderwertig*. Osler has said that the members of some families are born with poor tubing. The defect need not express itself in identical ways in all the members of a family. It may be angina pectoris in one, apoplexy in another, myocarditis in a third, and coronary occlusion in a fourth. For example, the mother of one of my patients with coronary occlusion which proved fatal, died of Adams-Stokes disease; another lost a brother with coronary occlusion, and had a sister suffering from mitral stenosis who developed pneumonia and died of spreading gangrene of the extremities.<sup>1</sup> The famous case of the Arnold family is well known.

2. A second factor is *mental strain*. This may explain the anomalous fact that angina pectoris is a rare disease in public hospitals, the patients of which are largely recruited from those who labor with their hands more than with their brains.

3. *Overeating*.—This, I think, is a very fruitful cause. It usually leads first to hypertension and then to disease of the coronary vessels.

4. *Tobacco*.—For some men tobacco is a poison. It might not be if used in moderation, but if used in excess it certainly in my opinion is harmful and in those who are predisposed racially or familially to arterial disease, whether it be of the extremities or of the heart, tobacco even in moderate amounts is injurious.

5. *Syphilis*, while important as a cause of aortitis and aneurysm of the aorta, does not, in my experience, occupy a prominent place among the etiologic factors of coronary disease or coronary occlusion. If it did play a significant rôle, one would expect to find coronary occlusion frequently in hospital patients, especially in negroes in whom lues is so common.

<sup>1</sup> Riesman, Med. Clinics of North America, Philadelphia, January, 1923, vi, 861-870.

Neither Hines<sup>1</sup> nor Wearn<sup>2</sup> found syphilis a factor of importance in coronary thrombosis and infarction. Scott,<sup>3</sup> on the other hand, found one-fourth of his cases dependent upon syphilis.

While I do not believe that syphilis is important in the etiology of coronary disease under ordinary circumstances, I think that it is a factor in cases of the affection occurring in early life, *i. e.*, under the age of thirty-five.

6. One other factor of possible importance in the production of coronary disease is *focal infection*. I have seen evidence to the effect that disease of the gall-bladder may produce anginal symptoms of a severe character and that these symptoms are abolished by the removal of the gall-bladder.

Coronary thrombosis is more common in men than in women, the male preponderance being greater than it is in ordinary angina pectoris. Some have said that women do not die of coronary occlusion, but I have seen it happen. (See Case II.)

While a disease of middle and advanced life, the majority of deaths occurring between sixty and sixty-nine,<sup>4</sup> cases in very early youth are on record. Klemperer<sup>5</sup> reports a case of coronary sclerosis with rupture of the left ventricle in a girl of thirteen.

Regarding occupation, I would say that in my experience, business men came first, then physicians, then lawyers, and then housewives. In White's 62 cases<sup>6</sup> the distribution was as follows: business men, 26; housewives, 10; physicians, 8; artisans, 5; lawyers, 2; engineers, 2; others, 9.

The symptoms produced by closure of a coronary artery depend upon:

1. The rapidity of the closure.
2. The size of the vessel occluded.
3. The state of the myocardium.
4. The potentialities of the collateral circulation.

Slow closure, especially of a small branch, produces de-

<sup>1</sup> Medical Clinics of North America, September, 1924.

<sup>2</sup> Amer. Jour. Med. Sci., 165, 1923, 250.

<sup>3</sup> Transactions of the American Association of Physicians, 1924.

<sup>4</sup> Nathanson, Amer. Jour. Med. Sci., 170, August, 1925, 240.

<sup>5</sup> Berlin Letter, Lancet, January 3, 1925, p. 47.

<sup>6</sup> Jour. Amer. Med. Assoc., 87, November 6, 1926.

generative and fibroid changes in the myocardium which may or may not give rise to signs that are clinically recognizable as of coronary origin, although they may be revealed by the electrocardiograph.

Sudden closure produces symptoms of great violence and of extraordinary gravity. When the vessel is a large one or if the heart has been the subject of long-standing disease, death may be instantaneous or it may follow after a short interval.

Coronary occlusion with its sequels, infarction and myomalacia cordis, is the most common cause of rupture of the heart.<sup>1, 2</sup>

**Symptomatology.**—In describing the symptomatology I shall confine myself to that of acute, sudden closure of a coronary vessel.

The patient is usually a man past fifty years of age, often thick necked, heavy set, and of florid complexion, who has for some time had either definite seizures of angina pectoris or slight attacks of cardiac oppression with eructations of gas. In rare instances the previous history is devoid of suggestive features; or there may have been one or two remote attacks of severe angina pectoris—perhaps themselves the result of occlusion of a small coronary branch.

A patient of the type described is seized suddenly with an unendurable pain, in its devastating severity unlike anything he has ever experienced before. His face becomes ashen, exsanguined, and pinched. A cold sweat breaks out over his face and body. The extremities are cold, the pulse is small—it may be regular, of normal rate or even slow<sup>3</sup>; usually it is rapid and thready. If the patient survives the attack the pulse may remain rapid for days and weeks. The heart-sounds are feeble; the first sound at the apex may be scarcely perceptible. Frequently, a murmur—not heard before—is found

<sup>1</sup> Locke, *Med. Clinics of North America*, May, 1925.

<sup>2</sup> Lewis (*Ann. Clin. Med.*, July, 1925) reports 7 cases of rupture of the heart among the insane.

<sup>3</sup> Oppenheimer and Mann (*Cardiac Arrhythmias*, New York, 1925) have noted marked bradycardia after thrombotic or embolic closure of a coronary artery.



at the mitral area or over the body of the heart. Respiration is shallow and restricted due to the fact that the patient is afraid to breathe just as he is afraid to make any unnecessary effort. Sometimes there is intense dyspnea or the breathing is of the Cheyne-Stokes type. Râles may be heard over the bases of the lungs; sometimes pulmonary infarction occurs. The whole condition is one of profound physical and mental shock. This is borne out by the state of the blood-pressure, which will often fall precipitously as much as 60 to 80 mm. or more. I have seen it drop from 220 to 90 systolic in the course of a few hours in a patient who nevertheless recovered.

The pain is unspeakably intense and is not relieved by nitroglycerin and scarcely by morphin in large doses. It is of a crushing, crunching, or tearing character and may be situated behind the upper, middle or lower sternum, in the precordia in the region of the parasternal lines on both sides of the chest, or in the epigastrium. It may radiate to one or both arms or to the upper back or it may not radiate at all. In several of my cases the pain in the left elbow was even more severe than the sub-sternal pain.

It is not surprising that the patient is in the highest state of angor mortis. He is panic-stricken by the fear of death; yet there are many individual differences in this respect. After all, a patient's state of mind depends on his character, temperament, and racial background. While the majority are paralyzed by the fear of death, others have no such fear. They realize that their time has come, but are unafraid and calm except in so far as the agony of pain may force a moan from their reluctant lips.

I made mention of the fact that the pain may be epigastric. Sometimes it is accompanied by vomiting and marked distention, so that it may simulate very closely an acute abdominal catastrophe, such as perforation of an ulcer, biliary colic, acute pancreatitis, mesenteric thrombosis, or the gastric crises of tabes.

Either the intensity of the pain or the disturbance of the cerebral circulation may cause syncope at the beginning of the

attack or convulsions toward the end. The temperature falls at the onset, but soon rises to 100° or 102° F. It is probably caused by the absorption of proteins from the infarcted area of the heart. There is usually a leukocytosis which, as Libman has shown, is detectable as early as one and three-quarter hours after the onset of the attack.<sup>1</sup> It may reach as high as 30,000, but usually ranges between 12,000 and 20,000. If the leukocytosis persists or increases in the absence of a responsible complication, it indicates progressive necrosis or intraventricular thrombosis, or both. Progressive necrosis may lead to acute aneurysm or to rupture of the heart.

If the obstructed artery is the anterior coronary, a small patch of to-and-fro pericardial friction may be detected, corresponding in all probability to the area of infarction. The pericarditis not rarely, however, extends far beyond the infarcted area. Enlargement of the liver, which is quite common, is indicative, in the absence of congestive heart-failure, of closure of the right coronary artery. Slight jaundice has been observed in a few instances; albuminuria usually occurs and, in rare cases, sugar appears in the urine.

Although in many cases the attack of coronary occlusion follows effort, in several I have observed the acute seizure was precipitated by no actual physical cause. In some the attack began on the golf links, in some at night after a particularly heavy dinner, but neither the meal nor the play could be looked upon as unusual for the patient. Yet in several of the cases I have in mind the attack proved fatal.

While the picture I have sketched above is the most common, coronary occlusion may cause instant death without preliminary agony or evidence of pain. Such apparently painless deaths are by no means uncommon. They occur most often in those in whom attacks of characteristic anginal pain have given warning—a warning that was not always heeded or understood. Until the autopsy it is impossible to tell whether such a sudden death is due to a real coronary obstruction or to angina pectoris without actual obstruction—which goes to show how

<sup>1</sup> Libman, *Amer. Heart Jour.*, i, October, 1925.

closely in their pathologic physiology angina pectoris and coronary occlusion are related. What is commonly called "status anginosus" is most often a progressive coronary occlusion and not simply cumulative attacks of angina pectoris.

The electrocardiogram may give valuable information. We have learned through the work of Willius, Pardee, Rothschild, Oppenheimer, Mann, M. H. Kahn, and numerous others that acute coronary disease produces recognizable changes in the Q.R.S. complex and in the R-T interval and in the origin and position of the T wave. Inversion of the T wave in a single lead or in all leads must be found unrelated to digitalis administration to be of significance, for digitalis itself may cause quite similar inversion. If the patient recovers, these abnormal responses may continue for some time after the subsidence of the attack. However, the changes described are not constant.<sup>1</sup>

Congestive heart-failure may follow an attack of coronary occlusion. If the congestive failure continues, pain may remain in abeyance. This is in line with an observation of the late Dr. J. H. Musser. He found that angina pectoris would disappear when dilatation of the heart supervened. In cases of decompensation secondary to coronary occlusion, feebleness of the heart-sounds and rapid or irregular pulse or gallop rhythm, as well as a leaden hue of the countenance, remain as suggestive features of the coronary block.

In some cases of coronary occlusion, after a twenty-four- or thirty-six-hour period of profound collapse, during which life seems to hang in the balance, the patient being perhaps in a stupor, there is a sudden, almost miraculous improvement in the symptoms, giving rise to the hope that all danger is past. Such hope, unfortunately, is not often well founded—the patient while talking cheerfully may suddenly drop back dead. It is usually possible in this tragic type of case to detect during the interval of *bien-être* the objective signs of gravest myocardial damage.

Aside from the severe cases from which recovery is exceptional, there are undoubtedly milder cases in which a small twig

<sup>1</sup> Longcope, Ill. Med. Jour., 41, 186-192, March, 1922.

instead of a large branch of a coronary artery is occluded. The symptoms are those of angina pectoris, but they persist longer and leave the patient in a state of exhaustibility with signs and symptoms of a damaged myocardium. In time these effects may disappear. After recovery the countenance retains its sallow pallor for a long time; the patient drags himself along at a slow gait and exhibits in every direction a marked lessening of vitality.

What is the relation of coronary occlusion to angina pectoris? Personally, I hold the view that angina pectoris is a "coronary affair"—*une affaire coronaricenne*, as the French say. It differs from true coronary obstruction in the fact that there is in angina pectoris no organic, at least no permanent closure of a coronary vessel. There is, however, a temporary closure due to spasm, with consequent histanoxia.

I am aware of the controversial nature of this subject, but as I am dealing in the present essay with actual coronary obstruction and not with ordinary angina pectoris, I shall omit further discussion of the pathogenesis of the latter affection.

Adams-Stokes disease when not due to gumma is usually caused by fibroid changes in the conduction system.<sup>1</sup> As these changes are usually secondary to sclerosis of the small coronary branches that supply the two principal nodes or the bundle of His, it might seem germane to the subject of this paper to include Adams-Stokes disease, but nosologically it is such a distinct and different affection that it is proper to omit its clinical discussion here.

I shall now cite a few cases of coronary obstruction that illustrate the principal symptoms.

Case I.—J. M. H., widower, aged fifty-nine years, was seen in consultation with Doctors Long and Mengel of Wilkesbarre. While sailing along the coast of Maine he was caught in a storm and thoroughly drenched. He had some difficulty in landing, but succeeded after a considerable effort. The next day he was seized with pain first in the right, then in the left, chest. A physician was called, who found his systolic pressure 170; the temperature 101° F.; two days later the blood-pressure was 100, the temperature 99° F. The pulse was irregular and of poor volume; the skin was covered with a

<sup>1</sup> This condition might for the sake of brevity be designated as "hisisit."

profuse sweat. He remained in bed four weeks and was then brought in a private car to his home in Pennsylvania. He tried to walk about the house and grounds, but a recurrence of the pain forced him to go back to bed. When I saw him, about six weeks after the onset, he was still having prolonged periods of precordial pain. He disclaimed any fear or anxiety as to his condition, but his actions and his facial expression indicated more plainly than words how greatly he was alarmed. Upon inquiry it was found that some weeks before going to Maine he had had pain in both shoulders and arms, especially in the left arm, which was thought to be muscular. He was a dynamic individual, with heavy managerial burdens that had been greatly aggravated by the coal-strike. I might add that x-ray, blood, blood-chemistry, and urine were normal; the Wassermann negative. Physical examination showed a somewhat enlarged and rapid heart, with a gallop rhythm of the anapest type. There was no murmur. Lungs and abdomen were negative. There was a slight elevation of temperature up to 100° F. This subfebrile condition continued for about two months. The blood-pressure varied from 108 to 130 systolic and from 60 to 90 diastolic. An electrocardiographic examination was made by Dr. S. Calvin Smith and gave the following results: "There is evidence of coronary artery defect in the heart records. The T wave is inverted in Lead I, the R wave in Leads II and III, and the T wave flat in Lead II."

At the end of four or five months I saw the patient again; he was much improved, although he had not entirely regained his pristine capacity. There could be little doubt as to this patient's case—we all concurred in the diagnosis of coronary obstruction which had been made by Dr. Cues who saw him during his attack in Maine.

**Case II.**—Mrs. C. W., seen with Dr. Donnelly, of Conshohocken, Pa., was a widow, fifty-two years old. She had had heart trouble for many years. Ten days before my visit she had an apparently definite seizure of angina pectoris. In speaking of the attack she said: "I thought I would go insane with the pain." She had had five attacks in one day; since then the precordial pain had been increasing steadily. Her blood-pressure during the first seizure was 60 systolic and 40 diastolic. I found her in a condition of extreme shock with a pale, frozen look, with a blood-pressure of 86 systolic, feeble heart-sounds, a soft systolic murmur and a definite patch of pericardial friction. The liver was enlarged and had a tender edge; the lungs were clear. It was evident that the end was near; the patient died before the close of day.

In this case the very first attack, which gave the impression of angina pectoris, was probably due to the closure of a large branch of the coronary artery with infarction of the heart.

**Case III.**—Mr. T. S. G., a widower, sixty-two years of age, was seen in consultation with Dr. J. T. Ullom. Mr. G., a short, florid, heavy-set man, had always enjoyed good health. On October 12, 1925 he ate a hearty dinner, ending the big meal with a large quantity of nuts. The next day he experienced a little substernal pain reflected into the left arm. At 11 p. m. a dull ache in the precordial area caused him to send for Dr. Ullom, who

administered morphin. The pain was somewhat abated, but returned at 4 A. M. with much greater severity. The blood-pressure was 160 over 100; the urine contained albumin and granular casts. Morphin was again given hypodermically, but brought no easement of the pain.

I had the opportunity of seeing the patient a few hours later—his systolic blood-pressure was from 120 to 130, the pulse 132. I was asking the patient a few questions, when suddenly he became purple and dropped back dead. Artificial respiration and adrenalin intracardiacally were of no avail. In this patient the fatal attack, which covered all in all a period of about thirty-six hours, was apparently the first the man ever had.

Case IV.—M. A., aged forty-five years, had been well except for several attacks of sciatica. He was once told he had diabetes, but many examinations of the urine made afterward failed to show sugar. The postwar collapse imposed heavy financial losses upon him—the resulting nervousness caused him to smoke excessively, something he had never done before. On October 5, 1921, while in a department store, he suddenly had a queer sensation in his chest which rapidly changed to a pain of increasing severity. On arriving home he sent for a physician, who tried amyl nitrite and morphin, but without success. Finally, chloroform was administered—it stopped the pain, but only as long as the patient was under its influence. When I saw the man with Dr. Clyman and Dr. Rosenfeld two days after the onset of the attack, the pain was unmitigated—it was most severe in the center of the upper chest, a little less severe in the precordial region. The blood-pressure which had been as high as 200, had dropped to 84 systolic; I found it 110. The heart was a little enlarged to the left, the sounds feeble; pulse 100; temperature 101.4° F. The liver was a little enlarged and tender to touch. Râles were present at the bases of the lungs. The pulse in the dorsalis pedis arteries was absent. The face had a pale leaden hue, the lips were almost greenish in color. The whole picture was that of the most profound shock.

As from a medicinal standpoint nearly everything possible had been done, I ordered the application of leeches to the precordia. Almost immediately the pain began to disappear. General improvement was slow, but eventually the man's condition approached his norm. A year later, however, he had another attack, even more severe—this time with a definite pericardial friction. He asked to have the leeches reapplied—it was done, with the same result.

The man is still living, six years after the first seizure, having in the interim passed through a severe attack of pneumonia. His case which I have previously reported<sup>1</sup> is made doubly interesting by the fact that a brother died in an attack of acute coronary obstruction, the terminal event being a convulsion.

Case V.—F. F., aged sixty-six years, was seen with Dr. Major on March 29, 1927. The man, a hard worker and an equally hard player at golf, had

<sup>1</sup> Med. Clinics of North America, Philadelphia, January, 1923, vol. vi, 861-870.

never been seriously ill. On Sunday, March 27, 1927, he experienced "a little indigestion feeling" and a soreness in the right arm on putting on his coat. He started to play golf and had driven three balls when he felt pain in both arms and lower sternal region and broke out in a profuse sweat. He lay down in the club-house and the sensation passed off. Thereupon he went home. During the night he was seized with terrific pain in the left arm, epigastrium, and lower sternal region. He was a little short of breath, due, he thought, to the soreness. Under morphin he was comfortable until Monday evening, the 28th. Then the pain recurred and would not yield. When I saw him on the following morning, the pain, now of moderate severity, was located in the midline between the xyphoid and the umbilicus. The heart-sounds were weak; there was no murmur, only an occasional extrasystole; the lungs were clear; the abdomen negative; the reflexes normal; the prostate enlarged. The blood-pressure was 134 systolic, 80 diastolic, pulse 100.

When I asked the patient whether he smoked, his answer was: "I smoke like the devil." Dr. Major and I enjoined absolute rest, but the patient insisted upon going to the toilet later in the day and dropped dead, forty-eight hours after the onset of the trouble. I believe that what he called an indigestion feeling was the actual beginning of the coronary closure.

**Differential Diagnosis.**—In the beginning the attack might readily be considered one of angina pectoris, but (*a*) the persistence of the pain; (*b*) the profound shock; (*c*) the enfeeblement of the pulse; and (*d*) the fever soon point to the graver condition.

When the pain is in the epigastrium or elsewhere in the abdomen, the possibilities of error are manifold. Biliary colic, perforation of a peptic ulcer, acute pancreatitis, mesenteric thrombosis, and the gastric crises of tabes are some of the false diagnoses that may be made.

It is impossible to lay down absolute criteria of differentiation—the important thing is always to have in mind the various possibilities when one sees a patient who is in profound shock and suffering from agonizing pain in the upper abdomen.

As a rule, the fear of impending death, the *angor mortis*, is greater in coronary occlusion than in other conditions. Moreover, there is often a history of previous anginal attacks; a to-and-fro pericardial friction points strongly to cardiac infarction; the electrocardiograph may help. In coronary thrombosis with abdominal symptoms, there is only transient rigidity, even though the tenderness may persist. Preservation of the liver dulness militates against perforation of a peptic ulcer.

Sometimes it is extremely difficult to decide between coronary occlusion and biliary colic. This fact has been emphasized by Faulkner, Marble, and White.<sup>1</sup>

As a rule, the gall-stone cases are younger and the history of painful seizures somewhat longer. Arm radiation of the pain, poor heart-sounds, and arrhythmia are in favor of coronary thrombosis; back radiation and jaundice of biliary colic. Jaundice may, however, occur also in coronary obstruction.

The resemblance between coronary occlusion and acute pancreatitis is often exceedingly close. Aside from the various points already mentioned, it is well to bear in mind that the spleen may be greatly reduced in size in the latter affection. I have also noted a peculiar subcyanotic hue in acute pancreatitis.

The electrocardiograph may prove helpful in the differential diagnosis, but, as I have pointed out, the alterations attributable to coronary occlusion are not invariably present.

There is one objective finding to which I have learned to attach a good deal of significance, namely, absence of the dorsalis pedis pulse. It is indicative of a wide-spread endarteritis and constitutes circumstantial evidence of coronary disease.

Pneumothorax may cause acute pain in the precordial area closely resembling an attack of angina pectoris or, in rare instances, a coronary occlusion. I have seen one case of this type. The man was a builder, and while on his job he was suddenly seized with violent pain in the left chest. His physician was sent for and diagnosed angina pectoris, but the pain persisted and did not yield to ordinary measures. When I saw him the man was in partial shock; careful physical examination showed pneumothorax which had come on after he had lifted a heavy weight.

Brachial neuritis of the left side may, in rare instances, resemble anginal attacks or attacks of coronary closure. The pain may be very severe. The absence, however, of pain in the precordia and the lack of evidence of any cardiac weakness, the presence of marked tenderness over the brachial plexus—

<sup>1</sup> Jour. Amer. Med. Assoc., December 27, 1924.



on pressure above the clavicle—guide the diagnosis in the right direction.

**Prognosis.**—Coronary occlusion accounts for a large number of sudden deaths, particularly for many of the deaths that the newspapers ascribe to acute indigestion. Recovery is possible in bad cases, and sudden death may occur in those that seem to be on the road to recovery. One must, therefore, be guarded in one's prediction. Persistent feebleness of the heart-sounds and increasing pulse-rate justify a grave prognosis.

The pain itself is not a good criterion—it may be as severe in occlusion of a small as of a large branch. In the case of the former, collateral circulation may be established and the patient recovers. The occurrence of definite decompensation usually means that the attacks of pain are at an end; but as the heart has been badly damaged by the coronary thrombosis, the outlook for eventual recovery is not good.

An individual who has recovered from an attack of coronary obstruction is always in danger of another, although the attack may remain in abeyance for a long time. In one of my cases there was an interval of seven years between the first and the second attack—and that proved fatal.

**Treatment.**—This naturally divides itself into two parts—treatment of the attack and treatment of the interval. During the attack there is but one overpowering indication—to relieve pain. Unfortunately morphin in reasonable doses is often powerless to do so. The Germans have recommended papaverin, a derivative of opium which is supposed to have the quality of dilating the coronary arteries. I have used it a few times without much success. Sometimes heroin, the importation of which should never have been stopped, acts fairly well. Chloroform has been used, but if an anesthetic has to be employed, I should give the preference to ethyl chlorid.<sup>1</sup>

I have mentioned above the case of the patient in whom we applied leeches and who, in a second attack, at once asked

<sup>1</sup> Lately diathermy has been recommended. I have had no personal experience with it.

that they be applied again. It is, to be sure, a somewhat fantastic remedy; I cannot explain the good results it accomplished in that patient's case, but whenever leeches are available there can be no harm in using them. A large number is required—the precordial area should be pretty well covered.

Absolute rest is a *sine qua non*—in no affection is it more important. External heat should be applied; the room should be kept dark and all disturbances eliminated. Whisky or, when there is much distention, brandy may be given.

What about the use of digitalis? There is here a difference of opinion among clinicians.<sup>1</sup> My personal practice has been to withhold digitalis or to use it only in minimal doses at the beginning of the attack. I have had recourse to caffein sodio-benzoate, to camphorated oil, and to adrenalin, reserving the digitalis for a later period—for the weakness following the acute attack or for congestive myocardial failure.

If distention is marked, one may use, in addition to brandy, turpentine stupes, the rectal tube, or pituitrin.

The diet is important—I have found buttermilk and acidophilous milk better than ordinary milk. If there is vomiting, iced buttermilk or iced ginger ale is best.

I have usually prescribed sodium citrate in 1-gm. doses, three or four times a day, believing it might prevent the formation of larger clots. It may of course have no such action when administered by the mouth.

**Interval Treatment.**—The patient should be kept in bed for three or four weeks or longer and, as Sir Clifford Allbutt eloquently expressed it, he should crawl before he walks. For the remainder of his life he should make it a practice to lie down for an hour's rest in the afternoon. He should never hurry, least of all after eating. Smoking, except in greatest moderation, is forbidden.

If need be, the bowels should be regulated with mineral oil or other mild laxative. The diet should be one low in protein and salt; starches and other foods productive of gaseous distension should be restricted. Overeating, especially at the

<sup>1</sup> See Harry Gold, *Arch. Int. Med.*, 1925, 35, 482.

evening meal, should be avoided. If there is obesity, a careful attempt should be made at weight reduction.

**Surgical Treatment.**—Whatever may be the ultimate position of the operation devised by Jonnesco for angina pectoris, namely, section of the cervical sympathetic, I do not feel that the operation is indicated or warranted in cases that are definitely diagnosed as advanced coronary disease or as coronary obstruction. The operation at best only does away with the pain. It does not remove any organic disease in the heart. Patients that have been operated upon for angina pectoris have died a painless death from coronary obstruction.

**Exercise.**—None should be taken for some time after the attack. Walking and golf on a non-hilly course may be permitted after a few months.

In all cases search should be made for foci of infection and their removal attempted if a possible connection between the focus and the disease of the coronary vessels can be established—provided, of course, that the procedure does not involve an unwarranted risk.

And finally, every patient who has gone through the agony of a coronary seizure should remember the words of John Hunter: "My life is in the hands of any rascal that chooses to plague me."

CLINIC OF DRS. GEORGE W. NORRIS AND  
DAVID L. FARLEY

PENNSYLVANIA HOSPITAL

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MYELOID LEUKEMIA

SKILL in arriving swiftly and surely at the diagnosis of disease not rarely is skill in the selection of the clinical or laboratory test best adapted to the problem under consideration. We are not able to have all the special tests at our command in every case we see. Skill in selection of the proper studies to be made is dependent upon knowledge of the symptoms and signs peculiar to disease groups. The need for a working classification in the mind of the physician then is evident. Diagnosis is classification. This point of view might be stressed, since our tendency is to consider classification schemata as uninteresting skeletons erected by medical pedagogues for their own abstract guidance in delivering a course of lectures. As a matter of fact, every practising physician sooner or later, consciously or unconsciously, necessarily erects his own working classification of diseases. He erects a more efficient structure if he be conscious of its practical importance.

This patient illustrates that we must think backward from major symptoms to group classification of disease. He also illustrates the frequent simplicity of a complete diagnosis when the proper test is selected. Mr. B. will give us the history:

MR. B.: The patient is a colored male, aged thirty-eight, who complains of pain in the back, epigastric fulness and tightness, general weakness, loss of weight, and shortness of breath. He was admitted May 11, 1928.

DR. NORRIS: Which, from his point of view, is his major complaint?

MR. B.: The pain in the back.

DR. NORRIS: Pain or discomfort is usually the symptom which causes the patient to seek medical attention. A history of pain should be exhaustive. Sufficient time should be taken where the diagnosis is in doubt to elicit every possible detail of pain.

Present Illness.—The patient was well until nine months ago, when pain developed in the back. The pain was dull, aching in type, did not radiate, and was more marked at the end of the day. It has increased somewhat in severity. At times it is not present. It is relieved to some extent by lying down. There is a sense of fulness in the abdomen, especially in the epigastric region. He has no eructations of gas or other symptoms of indigestion. The appetite is fairly good. General weakness has been gradually increasing. He has lost about 20 pounds in weight during the past nine months. There is occasional stiffness, but he has never had swelling of the joints. No edema of the legs has been noticed. Moderate shortness of breath occurs on slight exertion.

He has not had night-sweats, chills, or fever. He has no symptoms referable to the respiratory system. Since the onset of his illness he has had to urinate four or five times at night and ten or twelve times during the day. There has been no pain on urination, no burning, and no blood in the urine. He has not had headaches and mentions no symptoms referable to the central nervous system.

DR. NORRIS: You have not exhausted the history of pain. Is the pain in the back unilateral or bilateral?

MR. B.: The pain is present equally on the two sides. The patient points to an area between the sacro-iliac joint and the twelfth thoracic vertebra.

DR. NORRIS: What has been done as regards treatment? Some diseases are caused by treatment. Three years ago we had in the wards of the hospital a boy with anemia, paraplegia, and edema caused by Fowler's solution given by his physician over a prolonged period.

MR. B.: As far as we know there has been no treatment other than home remedies.

**Previous Medical History.**—He had measles and whooping-cough in childhood. In 1916 he had pneumonia with an uneventful recovery. He denies venereal disease. There have been no operations.

**Family and Social History.**—His father, mother, wife, and two brothers are dead of unknown causes. He has one child living and well. He is a laborer. He has not worked since October, 1927. He uses alcohol, coffee, and tobacco in moderation.

**DR. NORRIS:** What possibilities have occurred to you as an explanation of this combination of symptoms?

**MR. B.:** A local abdominal or spinal lesion might account for the pain, loss of weight, and abdominal fulness. Frequent urination and pain in the back suggest a genito-urinary lesion.

**DR. NORRIS:** Yes, that is true. I believe we can get no closer to diagnosis without further data than to say that there is a chronic disease. What was found on physical examination?

**Physical Examination.**—The patient does not appear to be acutely ill. The pulse is 80 at rest. The blood-pressure is: systolic 130, diastolic 85. The skin is free from eruptions. The scalp shows no abnormalities. The eyes appear to be normal. The cranial nerves seem to function properly. The mouth and nose and accessory structures show no abnormalities. The thyroid is not enlarged. There is no cervical lymphadenopathy. The chest is thin and flat, especially at the apices. Expansion is equal but poor. The lungs throughout are resonant to percussion. Breath-sounds and whispered voice-sound are increased in intensity over both apices, but more marked on the right side posteriorly above the spine of the scapula. The apex-beat of the heart is palpable in the fifth interspace, 10 cm. from the midline. The left border of the heart is 11 cm. and the right border 3 cm. from the midsternal line. Rate and rhythm are normal. Examination of the abdomen shows the most striking feature. A very large mass is felt on the left side extending from the diaphragm to the right and below the umbilicus. It has a rounded border which is notched. It is quite firm in con-



Figs. 161, 162.—Anterior and lateral views, showing the outline of the greatly enlarged spleen in myeloid leukemia.

sistency. The liver and kidneys are not palpable. There is no ascites. The genitalia appear normal. The peripheral reflexes are of normal range. The lymph-nodes are not enlarged. There is moderate sclerosis of blood-vessels.

DR. NORRIS: There seems little doubt that the abdominal mass is a greatly enlarged spleen. This would account for the pain in the back and the dyspnea. The spleen occupies about half the entire intra-abdominal space. We have now sufficient data for tentative diagnoses. What possibilities are suggested?

MR. B.: Some of the possibilities suggested by the enlarged spleen are: Chronic malaria, Gaucher's disease, subacute endocarditis, a metastatic tumor of the spleen, a cyst of the spleen, and leukemia.

DR. NORRIS: Chronic malaria is a remote possibility; the history is unlike malaria. Gaucher's disease is extremely rare and can be diagnosed definitely only by microscopic study of sections from the spleen or lymph-nodes. The enlarged spleen of subacute infectious endocarditis is caused by emboli from the endocardium with the development of splenic infarcts. There are no physical signs of heart disease. This, however, does not absolutely rule out endocarditis, but makes it more unlikely. This patient, as far as we know, has had no fever, additional evidence against endocarditis. Metastatic tumors of the spleen of any great size are extremely rare. We would not expect a uniform splenic enlargement in the case of a metastatic tumor. Echinococcus cyst of the spleen occurs and might give a very large smooth tense tumor such as we have. Leukemia is the most likely possibility you have mentioned. At the present time where would you group this patient and what laboratory test, if you were allowed only one, would you select?

MR. B.: I would place it among the diseases of the blood and would have a leukocyte count—total and differential.

DR. NORRIS: Your most likely diagnosis then is leukemia? Which of the two types of leukemia would you select?

MR. B.: The fact that the spleen is usually so much larger in myeloid leukemia than in lymphatic leukemia favors the



myeloid type. The absence of lymph-node enlargement is against the diagnosis of lymphatic leukemia.

DR. NORRIS: Lymphatic leukemia at certain stages may show no marked enlargement of lymph-nodes. However, enlarged lymph-nodes are the rule in this type of leukemia and in contradistinction to Hodgkin's disease and lymphosarcoma the enlargement of lymph-nodes is general and not enlargement of a local group. Exceptions occur. Will you summarize the laboratory studies?

MR. B.: The Wassermann test is negative. Urine analyses have shown a specific gravity ranging from 1.011 to 1.018. A heavy cloud of albumin at times has been present. At other times no albumin was noted. Moderate numbers of hyaline casts have been noted. Tests for sugar have been negative.

x-Ray study by Dr. David Bowen revealed a marked increase in the hilus lung shadows, especially on the right side, having the general appearance of adenopathy and also scattered lesions in the apices which he thought possibly might represent tuberculosis.

Blood-chemistry: May 22, 1928. Sugar, 70 mg. per cent.; urea-nitrogen, 12.1 mg. per cent.; creatinin 1.0 mg. per cent.; chlorids, 580.0 mg. per cent. Phosphates, 5.1 mg. per cent.

Ophthalmoscopic examination (by Dr. W. T. Shoemaker): There has been a small hemorrhage in each eye marked now by pigment deposit.

Basal metabolism: May 23, 1928, +12; June 5, 1928, +6.

Blood-counts:

May 11, 1928.	Hemoglobin	Red blood-cells	White blood-cells
	6.5 grams (41%)	2,080,000	250,000

Differential count:

		Remarks:
Polymorphonuclears . . . . .	52%	The red cells show achromia, marked anisocytosis, and poikilocytosis. An occasional nucleated red cell is seen.
Lymphocytes . . . . .	2%	
Large mononuclears . . . . .	1%	
Transitionals . . . . .	0	
Eosinophils . . . . .	0	
Basophils . . . . .	2%	
Myeloblasts . . . . .	2%	
Myelocytes . . . . .	39%	
Unidentified . . . . .	2%	

May 27, 1928.	Hemoglobin 7 grams (45%)	Red blood-cells 2,420,000	White blood-cells 226,000
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Differential count:

Polymorphonuclears.....	5%	Red blood-cell achromia, poikilocytosis, and anisocytosis.
Lymphocytes.....	0	
Mononuclears.....	0	
Eosinophils.....	10%	
Basophils.....	5%	
Myelocytes.....	75%	

May 31, 1928.	Hemoglobin 8 grams (51%)	Red blood-cells 2,770,000	White blood-cells 320,000
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Differential count:

Polymorphonuclears.....	20%	Achromia, poikilocytosis, and anisocytosis.
Lymphocytes.....	1%	
Basophils.....	4%	
Eosinophils.....	13%	
Myelocytes.....	53%	
Transitionals.....	5%	
Unidentified.....	4%	

June 6, 1928.	Hemoglobin 8 grams (51%)	Red blood-cells 2,960,000	White blood-cells 249,000
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Differential count:

Polymorphonuclears.....	26%	Achromia, poikilocytosis, and anisocytosis.
Lymphocytes.....	1%	
Basophils.....	2%	
Eosinophils.....	5%	
Myelocytes.....	64%	
Transitionals.....	2%	

DR. NORRIS: The diagnosis then seems to be established. Let me repeat that many patients suffering from blood diseases go undiagnosed for considerable periods, not because the diagnosis is not easily arrived at by a blood examination, but because the indication for a blood examination is unrecognized. Mr. B., what are some of the outstanding symptoms of leukemia which would immediately suggest to your mind that a blood examination should be made?

MR. B.: An enlarged spleen, a general appearance of anemia, skin eruptions, priapism, and hemorrhages.

DR. NORRIS: The symptoms caused by the weight and

pressure of an enlarged spleen are frequently what lead the patient to first consult a physician. This was true of the patient presented today. Discomfort in the left upper abdominal quadrant may be present. Edema of the legs may result from pressure on the great vessels. The polyuria was no doubt due to pressure on the kidney. Dyspnea was due to diaphragmatic embarrassment and anemia.

The second symptom you have mentioned, general appearance of anemia, may or may not be present. This form of anemia is often called myelophthisic anemia, and is due to overgrowth of the myeloid cells in the bone-marrow with a lessened production of red blood-cells from crowding out of erythroblasts. We sometimes see the same type of anemia from the growth of metastatic tumor cells in the bone-marrow.

Skin lesions are usually eczematoid, purpuric, or actual small tumor-like infiltrations into the skin or subcutaneous areas. As a rule, they occur late in the disease, but may appear early. Priapism occurs rarely in leukemia. Due to its dramatic symptoms its frequency has been stressed unduly. It is caused by collections of myeloid cells about the sacral centers or to thrombosis of the corpora cavernosa.

Hemorrhages often direct attention to the disease. They may occur as a sudden persistent nose-bleed, prolonged bleeding following tooth extraction or some minor operation, or in the female as vaginal bleeding. A sudden blindness or deafness may be caused by hemorrhage into the eye or ear.

You have given the patient's basal metabolism as +12. Is this a usual figure in leukemia?

MR. B.: As a rule the basal metabolism is increased in leukemia when the leukocyte count is high. The increased metabolism depends upon the presence of young cells, which are more active in oxygen consumption. The absence of increase in metabolism is a point in favor of a slow chronic process, and indicates a better prognosis as to duration of life.

DR. NORRIS: Now let us consider some points about the blood-picture in this disease. Mr. B., where do the leukocytes normally originate?

MR. B.: The leukocytes fall into three groups: (1) Lymphocytes, large and small, which are derived from lymphatic tissue of the spleen and lymph-nodes; (2) granular cells, including the polymorphonuclears, the basophils, and eosinophils, originating from myelocytes; and (3) the large mononuclear and transitional cells whose origin has been disputed. An attractive theory is that they originate from the lining cells of blood- and lymph-vessels (the endothelial leukocytes of Mallory).

DR. NORRIS: In an ordinary blood-count there is little reason to separate large mononuclear and transitional cells, as they apparently are the same. The transitional cell does not represent a transition form of polymorphonuclear cell as originally thought, but the name has the stamp of tradition. There seems little reason also to separate large and small lymphocytes. In acute lymphatic leukemia the large lymphocytes are unlike normal large lymphocytes and are really young actively growing abnormal lymphocytes. Mr. B., will you tell us briefly how you would recognize the myelocytes under the microscope?

MR. B.: Myelocytes have three outstanding features. They are granular cells, containing large numbers of basophilic, eosinophilic, or neutrophilic granules; they have a round or oval nucleus usually a little to one side of the center; they are larger than lymphocytes or polymorphonuclears, or the red blood-cells. Large mononuclears often contain granules in their cytoplasm, but unlike myelocytes the granules are very scanty in number. They are called azur granules.

The stain ordinarily sufficient is Wright's modification of the Romanowsky stain. In some cases it is necessary to use an oxidase stain in order to see the granules. This is true of acute myeloid leukemia. The rule seems to be that the younger the cell, the more difficulty in staining the granules. When the disease is so actively acute that the mother-cells of the myelocytes, the premyelocytes, are thrown into the blood-stream, it may be impossible to distinguish the cells from young lymphocytes.

DR. NORRIS: Very good. Now I will ask Dr. Farley to give us a summary of the prognosis and treatment of myeloid leukemia.

DR. FARLEY: The prognosis of leukemia is always fatal. This, however, does not mean that we can dismiss the matter. How long may we expect our patient to live? Will he be incapacitated until death? The average duration of life is from two to four years. Some live much longer than this. Cases of ten to fifteen and even twenty years' duration have been reported. Irradiation treatment undoubtedly is of great value. It often improves patients apparently in a nearly hopeless condition to the point where they are able to resume their work. We have under observation at present a cabinet-maker who has been working steadily for two years after a course of irradiation. He illustrates why we do not rest content with a hopeless prognosis. The question is unsettled as to whether irradiation alters the time factor of the disease. Statistics (Minot's) seem to indicate that life is not prolonged by irradiation, but the patient is kept in much better physical condition during his course. Our hope is that irradiation methods may be so perfected that the disease can be entirely controlled.

Treatment may be summarized under five headings: Drugs, surgery, irradiation, non-specific protein therapy, and general care.

Benzol has been used extensively in myelogenous leukemia. It has a depressant action on the cells of the bone-marrow. It is a specific bone-marrow poison. Unfortunately, it is not selective and affects the cells forming the red blood-cells as well as those forming leukocytes, thus causing anemia. At the present time it is not being used to any great extent. Its beneficent effects are limited.

The only indication for surgery is the removal of the spleen to relieve symptoms of weight and pressure. Removal of the spleen has not altered the course of the disease. It, therefore, is a measure to be used only in the exceptional case. The patient should be prepared by irradiation and shrinkage of the size of the spleen before operation. In this hospital two cases have had splenectomy. There was very little beneficial result and no effect upon the blood-picture. It is a questionable procedure.

Irradiation is the treatment of choice in myeloid leukemia. Under proper irradiation the blood-picture may be made to become almost or sometimes quite normal, the patient's sense of well-being returns, the spleen decreases markedly in size, and the patient may be able to resume his work. The remission may last from a few weeks to a year or more. The Roentgen ray or radium may be used. A careful technic must be followed with constant checking of the treatment by blood examination. The effect of  $x$ -rays and radium seems to be essentially the same. Patients who have become resistant to the  $x$ -ray and no longer improve under it may yet improve under radium treatment. The basal metabolism may be used as a check on treatment. In the average case as improvement occurs the elevated basal metabolism is lowered in proportion. The technic of irradiation must be carefully followed. Irradiation sometimes causes injury if not properly done.

A striking improvement temporarily may occur after acute infections. This has led to the treatment of leukemia by inoculation with the plasmodium of malaria. The results have not been sufficiently good to warrant the treatment. The blood-picture may improve, but the previous condition returns quite rapidly after the malaria is treated.

Various radium salts have been injected intravenously. Some effect is produced, but such treatment is so difficult to control that this method cannot yet be approved.

The general care of the patient means that from time to time in certain patients blood-transfusions are necessary for anemia. Iron and arsenic medication are given when needed. The liver diet is given where secondary anemia exists. Fresh air and sunshine are good for the patient. Are there any questions?

STUDENT: I am somewhat confused on aleukemic leukemia. Will you outline the different types of leukemia?

DR. FARLEY: Aleukemic leukemia is a confusing but necessary term. For clearness of understanding we may think of aleukemia as representing two conditions: (a) the aleukemic phase of leukemia and (b) true aleukemic leukemia. In the

first case we see patients with the typical blood-picture of leukemia whose blood may become normal and remain so for a considerable period of time, after which it may return to the original condition. This aleukemic phase may be spontaneous or due to treatment. It occurs in both lymphoid and myeloid leukemia. The second condition, true aleukemic leukemia, is said to occur in both the myeloid and lymphoid types. To avoid confusion I will mention only the lymphoid type. In true aleukemic lymphoid leukemia the lymphatic tissue everywhere in the body shows the uniform hyperplasia of lymphoid tissue peculiar to lymphatic leukemia, but there is no excess of lymphocytes in the blood. The question might be asked, Why then is not such a condition lymphosarcoma? Lymphosarcoma is a local condition involving one group of lymph-nodes primarily, while leukemia affects all the lymphoid tissue. The pathologic histology of aleukemic leukemia is the same as that of leukemia; therefore aleukemic leukemia and leukemia are probably the same disease. It is useful to divide them because of the problem of diagnosis and because they react differently to treatment. To make the matter more confusing patients are seen with the local infiltrating tumor, lymphosarcoma, who have a leukemoid blood-picture. The condition is called leukosarcoma. To show that these confusing terms are necessary I will cite briefly the case of a woman recently admitted to the hospital. Her blood-picture was typical of pernicious anemia. This diagnosis would have been complete except for the fact that gastric analysis showed a hyperacidity—a truly remarkable finding in pernicious anemia. Three months later her leukocytes were 220,000 per c.mm., with 55 per cent. of myelocytes. The diagnosis then was clear. We had seen her first in a spontaneous aleukemic phase of myeloid leukemia.

Acute lymphoid and acute myeloid leukemia occur. Acute lymphoid leukemia is characterized usually by increase in large immature lymphocytes in the blood; acute myeloid leukemia by immature myelocytes or myeloblasts. The course in both cases is so different from the chronic types that many believe

the cause of acute leukemia is not the same as the cause of chronic leukemia.

We sometimes see myelocytes in the blood in acute infections and in blood diseases such as hemorrhagic purpura where there has evidently been a profound stimulation of the bone-marrow, but the pathology of true leukemia is absent. This condition is called stimulation myelocytosis. Another common source of confusion in diagnosis is the presence of agranulocytosis or relative lymphocytosis, but no actual increase in the total number of lymphocytes. We see this especially in acute aplastic anemia.





# CLINIC OF DR. O. H. PERRY PEPPER

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## A REVIEW OF OUR KNOWLEDGE OF THE ANEMIAS OF PREGNANCY<sup>1</sup>

A RECURRENCE of anemia in successive pregnancies of the wife of a colleague brought home to me my ignorance of this subject. The following short review is the result of my attempt to find assistance in the voluminous literature on this topic. Unfortunately, this literature is far from satisfactory; much of it antedates the day of modern hematology, and there is constant confusion between the so-called pernicious anemia of pregnancy and true Addisonian or primary pernicious anemia. Furthermore, the majority of the case reports have been incomplete both as to hematologic details and as to the sure exclusion of such important causes of anemia as puerperal sepsis. Other complications, such as syphilis, are seldom ruled out.

A case report has an importance far beyond its immediate interest in that it is from such unit reports that the ultimate composite disease-picture is built up. Incomplete case reports are worse than useless, while the careful recording of even a single case is of great value and deserves greater appreciation than is today usually accorded to it.

**Historical.**—The early interest concerning the anemias of pregnancy was closely interrelated to the subject of true pernicious anemia. Pregnancy was by some believed to be the starting-point of true primary pernicious anemia. From this grew the view that the severe anemias of pregnancy were truly pernicious, and this term has persisted to the present in this

<sup>1</sup> Read before the Hancock County (Maine) Medical Society, August 22, 1928.

literature, as the following quotations will show. One of the objects of this review is to discover what justification there is for considering the anemia of pregnancy as an entity, and a second to review the reported cases in the light of the modern criteria for the diagnosis of Addisonian or true primary pernicious anemia.

Even before Biermer in 1868 and 1871 had presented his famous reports on primary pernicious anemia, in which many of the reported cases were in pregnant women, and in which he stressed an intimate relationship between pregnancy and this form of anemia, Lebert, for example, and Gusserow, and in this country in 1842, Walter Channing<sup>1</sup> had written of severe anemia in pregnancy. A reading of the original articles leaves one with the feeling that while unquestionably anemia was observed during or after pregnancy, it is impossible to learn its cause or its type.

By 1905, when the American Edition of the Nothnagel System appeared under Stengel's editorship, the question of the relation of pregnancy to pernicious anemia was under active discussion. In the article on primary pernicious anemia by Lazarus of Berlin it was pointed out that the literature contained "scarcely any reports of primary pernicious anemia in the anamnesis of which pregnancy or the puerperium played a rôle." In fact, Lazarus knew of but one case (Laache, Case 9) in which a connection between the disease and a previous pregnancy could be assumed. On the other hand, Eichhorst, in 1878, attributed 29 of his series of 50 cases of primary pernicious anemia in females to pregnancy and childbirth. This was explained by other writers as being due to local conditions among the Swiss, from whom 22 of the 29 cases were drawn.

In 1908 Cabot, writing in Osler's System of Medicine, stated that 35 of the 1200 cases of primary pernicious anemia in his series began during pregnancy or shortly after parturition. As there were only 434 female cases in the series this would suggest that the relationship was present in 8 per cent. of female cases. Unfortunately, Cabot's series included not only his own care-

<sup>1</sup> New England Quart. Jour. of Medicine and Surgery, 1842, 1, 157.

fully studied cases, but those obtained from the literature and from unpublished records of friends. This resulted in sore mouth being recorded in only 159 of the 1200 cases, while in only 79 cases was the gastric acidity tested and "only in one of this number was hydrochloric acid found in any considerable quantity."

The stricter enforcement at present of certain criteria for the diagnosis of primary pernicious anemia makes us look with doubt on many of the older reports.

**More Recent Views.**—Sir William Osler,<sup>1</sup> in 1919, reviewed the anemias of pregnancy in his inimitable style. He divided the anemias into four groups:

I. Anemia from postpartum hemorrhage.

II. The severe anemias of pregnancy.

III. Postpartum anemia.

IV. The acute anemia of postpartum sepsis.

He avoids the diagnosis of primary pernicious anemia and points out that "though progressive and often pernicious, the anemia is caused by an agent which differs in one all-important particular from that which causes the anemia of Addison. When recovery takes place it is permanent, and the woman may escape in subsequent pregnancies."

A beautiful example of the acute anemia of postpartum sepsis is that reported by Cabot in which the presence of sepsis was not suspected. The red-cell count fell to 800,000 per c.mm. before death. If an autopsy had not revealed the true state of affairs the case would, as Cabot says, have been classed as puerperal pernicious anemia. The three instances quoted by Osler are not as spectacular, but they do illustrate one very important fact which is that severe sepsis of this type can be present without enducing any leukocytosis. In other words, one cannot argue in such a case that an absence of leukocytosis favors a diagnosis, for example, of Addisonian anemia. It is especially in severe sepsis with blood-stream infection that leukocytosis fails, and it is in these very same cases that anemia may rapidly become severe.

<sup>1</sup> Brit. Med. Jour., 1919, I, 1.

In the more recent literature on the anemias of pregnancy one of the most frequently quoted and best articles is that of Alder<sup>1</sup> (often misquoted Adler), whose classification is as follows:

I. Anemia with pregnancy:

- (a) Chlorosis.
- (b) Posthemorrhagic anemia.
- (c) Congenital hemolytic icterus.
- (d) Previously present primary pernicious anemia.
- (e) Leukemia, acute or chronic, myelocytic or lymphocytic.

II. Anemia from pregnancy:

- (a) Physiologic.
- (b) Pernicious type of anemia of pregnancy.

Alder states flatly that in the history of almost every instance of the pernicious type of anemia of pregnancy there occurs a reference to some previous chlorosis, severe anemia, syphilis, or other infection. Of 7 cases quoted by Naegeli from Beyer-Guriwitsch<sup>2</sup>: Lues and chlorosis were present in one, chlorosis in one, and severe bleeding following delivery in 2; in Roth's case, syphilis was present and also in Nauer and Sandberg's. Chlorosis was present in 3 of Esch's reported cases; in Jungmann's, severe bleeding had occurred at a previous pregnancy. Alder concludes that the so-called pernicious anemia of pregnancy develops only in the presence of a bone-marrow whose function has been previously damaged. It is not a true primary pernicious anemia from any toxins of pregnancy, but only the reaction of an impaired bone-marrow to the frequently pathologic but also even to the physiologic demands of pregnancy.

Aubertin<sup>3</sup> takes an opposing view. He does not hesitate to call the condition pernicious anemia. It comes on only during pregnancy, not from repeated pregnancies; it is caused by placental hemolysins and is cured, and cured only, by expulsion of the fetus. Its onset may be in the early months of pregnancy, but it is usually recognized in the seventh month. Its symptoms

<sup>1</sup> Zeitschr. f. Geburtsh. u. Gyn., 1924, 87, 505.

<sup>2</sup> In Diss. Zurich, 1912.

<sup>3</sup> Le Bull. Med., 1925, 39, 261.

include edema, ascites, dyspnea, and albuminuria; often it is misdiagnosed as a nephritic or cardiac condition. The spleen is enlarged more often than in other anemias; there is evening fever without infection and blood-cultures are negative. The anemia is of a plastic type; the red cells vary in size, there are normoblasts and megaloblasts. A difference from classical primary pernicious anemia is found in the higher white-cell count, and the increase in the percentage of neutrophils. A fatal outcome may occur during delivery or a few days after, or the process may become chronic with death delayed. Recovery may occur.

Aubertin's views are confirmed by Bardy,<sup>1</sup> who collected from various sources 68 cases (one duplication) which he reports under the term "pernicious anemia of pregnancy." An analysis of these cases fails to reveal one which meets the modern requirements for a diagnosis of Addisonian anemia. One cannot read these case reports without being impressed with the probability that syphilis was present in many instances.

Within the past few years the publications on various phases of this subject have continued to be numerous. Larrabee<sup>2</sup> reported 17 cases of severe anemia occurring in pregnancy and the puerperium; 7 with a secondary blood-picture recovered, of 8 with a pernicious blood, 4 were transfused, and these recovered; the others died—one was aplastic, one atypical. To him there is a sharp difference between the group with a secondary and those with a primary blood-picture.

Of the 8 cases with the "pernicious blood-picture" 2 are recorded as having "sore mouth"; no gastric analyses are recorded, and in none is there any note justifying the belief that posterolateral sclerosis was present. In one "attacks of pain and tingling in the arms" were present. Larrabee's classification is based on "the blood-count and picture" which is often an unsatisfactory criterion. Severe secondary anemia will often present many features of a "pernicious picture," and a high color-index is scarcely an infallible sign. It is only fair to em-

<sup>1</sup> Thèse Paris, 1923-24.

<sup>2</sup> Amer. Jour. Med. Sci., 1925, 170, 37.

phasize that Larrabee does not consider these cases with "pernicious blood-picture" as identical with true primary pernicious anemia of the Addisonian type; he makes this very clear and quotes views of others both pro and con.

This distinction is not always kept clear. For example, Rowland,<sup>1</sup> in discussing Larrabee's article, employs the term "primary" thus being committed to this origin of cases with "pernicious blood-picture." Rowland,<sup>2</sup> in 1924, reported 2 cases, one of which in his later article he states was "definitely of the pernicious or primary type." Rowland points out the confusion between the pernicious anemia of pregnancy and true Addisonian anemia. He states that "the spinal cord changes of Addisonian anemia have not been described in typical form in hemolytic anemia of pregnancy, although paresthesias and pains are common . . . the gastric achlorhydria is not absolute." Nevertheless, he concludes that the hemolytic anemia of pregnancy closely resembles pernicious anemia.

Minot's<sup>3</sup> case which he terms chronic hemolytic anemia, "the pernicious anemia of pregnancy," had some ill-defined numbness of the hands and feet, but her hematologic findings did not in any way justify a suspicion of true Addisonian anemia. No gastric analysis was reported, the Wassermann was negative. He believes that nearly always the differential diagnosis between an anemia of pregnancy and a true primary pernicious anemia can be made on the blood findings alone as in the reported case. He also agrees that the anemias of pregnancy are progressive without remission, but if cured do not recur. Murdoch,<sup>4</sup> however, takes the opposite view, basing his decision on the recovery of such cases. He employs the term "hemolytic anemia of pregnancy." In the 3 cases he reports there is nothing to suggest a true Addisonian anemia except perhaps the marked improvement which occurred in one woman on a high nucleoprotein diet.

<sup>1</sup> Ann. Int. Med., 1927, 1, 129.

<sup>2</sup> Jour. Amer. Med. Assoc., 1924, 82, 372.

<sup>3</sup> Med. Clinics of North America, 1921, iv, 1733.

<sup>4</sup> Ann. Int. Med., 1927, 1, 133.

Neale<sup>1</sup> classifies his first case as belonging in Osler's second group and his second in Group 3. This latter is that in which the cases resembling Addisonian anemia are found and Neale's Case 2 did have soreness of the tongue. The color-index, however, was 0.7 on the first count, but 1.2 on the second. The woman died ten weeks after admission; at autopsy no infection was found, the spleen was small, and red marrow was present in the femur.

Among the many cases reported very few have been studied from the point of view of the presence or absence of those features which constitute the syndrome of Addisonian or primary pernicious anemia. Gastric analysis is hardly ever recorded; Hoskin and Ceiriog-Cadle<sup>2</sup> do report achlorhydria in a woman of thirty whose blood-count four weeks after the normal delivery of a full-term healthy baby was red blood-cells, 1,870,000; hemoglobin, 28 per cent.; color-index, 0.8 and white blood-cells, 2600. Fever was present and a diagnosis of infectious endocarditis was ventured; after transfusion, however, the fever ceased and after several months the blood-count was about normal.

McSwiney,<sup>3</sup> in analysing 43 cases of various types of the anemias of pregnancy, points out that many of the changes in the blood-picture usually found in primary pernicious anemia occur in the more severe cases of anemia of pregnancy. He is also impressed with the frequent association of anemia in pregnancy with syphilis. Balfour's<sup>4</sup> larger series of cases gives us little help in the present problem, being largely concerned with an attempt to draw analogies between eclampsia and the anemias of pregnancy.

Running through the literature is the reiterated belief in some hemolytic toxin arising autogenously during pregnancy. Commonly it is referred to as a placental hemolysin (Aubertin, Minot, etc.), and the theory has even been offered that early in pregnancy an hemolysin is produced giving, as a rule, only a

<sup>1</sup> Birmingham Med. Rev., 1927, 2, 316.

<sup>2</sup> Lancet, 1927, i, 433.

<sup>3</sup> Indian Med. Gaz., 1927, 62, 487.

<sup>4</sup> Ibid., 1927, 62, 491.



slight anemia before its being neutralized by an antihemolysin. To a failure to produce the antihemolysin is attributed the more severe and progressive anemias. Schneider<sup>1</sup> considers these anemias as due to a specific blood-toxicosis of hemolytic origin. Nyfeldt's<sup>2</sup> experimental attempts to produce an analogous anemia in rabbits throw no light on the problem.

Unquestionably the evidence favors the view that the anemia is a hemolytic anemia, but there is no evidence to permit us to designate the hemolytic factor at work. Nor is there any report to suggest that the blood of the fetus is affected by the maternal hemolysin. Offergeld<sup>3</sup> suggests that in true primary pernicious anemia the fetus may show the same blood changes as the mother, while in the pernicious anemia of pregnancy the fetus escapes. The case which he reports is of great interest in that a patient "with apparently undoubted Addisonian anemia" became pregnant during a remission of the disease. Offergeld admits no doubt as to the nature of the anemia and in support of this view points to the sore tongue and the typical blood-findings. During the pregnancy, anemia became progressively more evident, megaloblasts became numerous, and in the thirtieth week a therapeutic abortion was performed. The child was born dead, having died just before delivery. Examination of the infant's blood is said to have revealed changes identical with those found in the maternal blood including numerous megaloblasts. The mother continued to become more anemic, died nine months later, and at autopsy it is said that findings proving the diagnosis of Biermer's anemia were discovered.

Smith<sup>4</sup> does not admit that the anemia is of a hemolytic type, but admits a probably toxic cause. Of his 8 cases, one had a gastric analysis which revealed an absence of hydrochloric acid, but improvement in several seemed to follow the administration of the acid by mouth.

<sup>1</sup> Zeitschr. f. Geburtsh. u. Gyn., 1927, 90, 487.

<sup>2</sup> Ugesk. f. Laeger., 1927, 89, 296.

<sup>3</sup> Zeitschr. f. klin. Med., 1926, 104, 473.

<sup>4</sup> Surg., Gynec., and Obst., 1925, 40, 223.

This short summary covers the available literature up to the present with the exception of a contribution by Allan presented at the Association of American Physicians' meeting this past spring. He is quoted<sup>1</sup> as having said that 3 per cent. of cases of chronic pernicious anemia start during or after pregnancy. This is not our experience at the hospital of the University of Pennsylvania as the following analysis of our cases will show.

**Analysis of Accepted Addisonian Anemia with Relation to Pregnancy.**—In the past few years at the University Hospital there have been studied 40 female cases of primary pernicious anemia or, as we prefer to call it, Addisonian anemia, which met every criterion for this diagnosis. An analysis of these for any possible relationship between pregnancy and the occurrence of the anemia leads to the conclusion that in not one of the 40 cases can this relationship be established. Eight of the 40 have never been pregnant; of the 32 remaining, 17 had passed the menopause before any symptoms of the anemia had developed. In this group of 17 cases there were 5 in which the symptoms of anemia appeared within two years after the menopause; and in 2 of these the symptoms of the anemia seem to be merged with those attributed to the menopause. If one were inclined to draw the deduction that the menopause was in some way related to the onset of the anemia, one would find some statistical support in this series, but one would have to be cautious lest one be misled by a disappearance of menstruation incident to the developing anemia, the patient possibly erroneously attributing to a supposed menopause the early symptoms of the anemia. In no case could one feel sure of any definite relationship. In the group in which the anemia appeared prior to the menopause, there was no case which would convince the critical reader of any relationship. One patient had had a miscarriage the year prior to admission, and the anemic symptoms were of about a year's duration. There had been no unusual hemorrhage at the time of the miscarriage and the patient could not relate the

<sup>1</sup> Jour. Amer. Med. Assoc., 1928, 90, 2060.

symptoms of the anemia to the period immediately following the miscarriage.

Another patient, aged forty-nine, had been anemic at her last pregnancy, ten years previously, but the symptoms of her present anemia were of less than a year's duration.

Classified among the cases of Addisonian anemia in the hospital records was found one which on critical analysis seems to present some question as to its proper classification. It is quite typical of the difficulties presented in this field.

**Case Report.**—E. B., thirty-seven years of age, was admitted in November, 1920, to Professor Stengel's Service of the Hospital of the University of Pennsylvania. Her chief complaint was extreme weakness, which had been present for the first time eight years previously when her first child was born dead. Following that delivery weakness and pallor had made their appearance, but had improved somewhat on the administration of iron a year later. Five years ago her second pregnancy had been followed by definite anemia, from which she again improved.

Five months before admission extreme pallor and weakness developed, and there was also some numbness of the fingers and some loss of weight. At this time antiluetic treatment was commenced for a serologically proved infection. The immediate cause of her entrance to the hospital was extreme weakness and an attack of fainting shortly before admission. Her previous history gave no additional evidence of the syphilitic infection, and the second pregnancy resulted in a living and healthy child.

The salient features of the physical examination included prostration, a lemon-yellow pallor with marked pallor of the mucous membranes, murmurs present in the veins of the neck and over the heart. The spleen was easily palpable; the sense of position in the legs and feet was markedly impaired, but vibratory sense was preserved. Laboratory examinations proved the patient belonged to Moss Type 2. The Wassermann was positive; gastric analysis done by the fractional method on two occasions failed to reveal any hydrochloric acid. The urine analysis gave no important findings. The blood examination for fragility of the red cells in hypotonic salt solution showed hemolysis to begin in 0.5 and to be complete in 0.4. Blood-counts are recorded in Table I; the table also includes the transfusions given and the findings after splenectomy and also upon a second admission three months after the first. This second admission followed a return of anemia, perhaps as a result of a profuse menstrual bleeding a month previously. At this time she became very weak, but had no return of the numbness.

Against the diagnosis of Addisonian anemia one can point to the luetic infection, the absence of glossitis, and the loss of vibratory sensation, and somewhat inadequate morphologic changes in the red cells. In favor of relating this anemia to pregnancy is its onset or at least its aggravation during or after each of two pregnancies. On the side of true Addisonian anemia, one

TABLE I

Date.	Hb.	R. B. C.	Reticu- lated cells.	W. B. C.	P.	L.	M.	Myel.	N. mor- pho- blasts Per 100 W. B. C.	Megalo- blasts W. B. C.	Morphologic changes in red cells.
11/17/20	21	950,000	....	4,400	70	23	7	1	3	4	+
11/20/20	..	Transfusion.	....	2,000	73	22	1	2	9	6	+
11/22/20	28	1,050,000	3%	2,000	50	43	5	..	8	5	+
11/26/20	19	930,000	....	3,900							
12/ 1/20	20	920,000	....								
		Transfusion 600 c.c.	....	4,600							
12/ 3/20	30	1,600,000	....								
		Transfusion 650 c.c.	....	4,100	75	21	3				
12/ 5/20	40	2,090,000	....								
		Transfusion 600 c.c.	0.5%								
12/ 8/20	42	2,510,000	....								
		Splenectomy.	....	11,300	67	19	13	..	3	..	(Platelets 390,000.)
12/ 9/20	60	2,400,000	1.5%	14,400	66	27	7	..	4		
1/ 6/21	60	2,840,000	....	7,900	40	54	4	..	8		
1/10/21	60	3,200,000	....	10,000							
1/18/21	60	3,010,000	....								
1/26/21	65	Discharged from hospital.	....								
6/ 2/21	55	2,630,000	....	10,200	..	..	..	..	..	..	(Count outside hos- pital.)
8/15/21	..	Profuse menstrua- tion.	....	.....	..	..	..	..	..	..	(Count outside hos- pital.)
	45	2,270,000	....								
9/27/21	45	1,600,000	....	10,000	..	..	..	..	..	..	(Second admission to hospital.)
9/30/21	48	1,500,000	....	9,000	39	58	2	..	16		(Platelets 312,500.)

may claim the achlorhydria, the long course with a possible remission, the high color-index, and the low white-cell figure in many of the counts. Whatever one's decision as to the proper classification of this case, it clearly illustrates the difficulties and confusion which attend this problem.

**Physiologic Anemia of Pregnancy.**—So far little has been said about the so-called physiologic anemia of pregnancy, although this has been assumed by many of the writers in this field. Alder includes it in his classification and, in fact, explains some of the more severe pernicious anemias of pregnancy as being the result of the physiologic demands of pregnancy on a hematopoietic system already below par for some reason or other. It is probably in this way that various factors such as syphilis, chlorosis, hemophilia with anemia, act in predisposing to severe anemia in pregnancy. De Lee<sup>1</sup> concludes that a previously chlorotic woman is apt to become more anemic in the early months of pregnancy probably as a result of the demands of the fetus for iron, but that hematopoietic activity usually soon restores the blood to normal.

Incident to this marrow activity there occurs a moderate leukocytosis, the so-called physiologic leukocytosis of pregnancy first described by Virchow. A recent review of Heyn<sup>2</sup> will supply detailed information for those interested.

Many studies of the so-called physiologic anemia of pregnancy have been reported in the literature, but most of these have been inadequate. Recently this subject has been reviewed by Kühnel<sup>3</sup> and a careful study of the erythrocyte count, hemoglobin percentage, and cell volume percentage in 15 normal healthy pregnant women made. Some of his observations commenced as early as the first week of pregnancy and continued up to a year after parturition. Kühnel found sufficient variation from normal to justify the claim for a true anemia of pregnancy. He found it difficult to date accurately the beginning of the anemia, but definite changes in hemoglobin, red cell-

<sup>1</sup> Principles and Practice of Obstetrics, 4th ed., pp. 105, 407.

<sup>2</sup> Zeitschr. f. Geburtsh. und Gyn., 1924, 87, 518.

<sup>3</sup> Ibid., 1926-27, 90, 511.

count, and volume per cent. are apparent before the eighth week of pregnancy. The anemia increases up to the sixteenth to twenty-second week, after which the figures remain stationary for two weeks. Often an improvement occurs between the thirty-second and thirty-fourth week, only to be again followed by a fall, especially in the hemoglobin. The lowered figures up to the thirty-fourth week seem in part, at least, to be due to hydremia, and the rise in count at about the thirty-fourth week to be explained by the diuresis which it is known occurs about this time. Kühnel even suggests that this thirty-fourth week rise is sufficiently constant to permit of its use as a help in determining the period of a given pregnancy. These observations showed no material differences in primiparæ or multiparæ. Nor did the variation differ from normal; the greatest variation in hemoglobin observed in the series was 27 per cent. and in erythrocyte count 25 per cent.

Immediately postpartum some degree of secondary anemia is the rule, with a greater reduction in hemoglobin than in red cell numbers. This "chloro-anemia" is very slow to disappear even after wholly uncomplicated pregnancy and delivery. All of Kühnel's patients continued anemic up to four to six months postpartum and some even up to twelve months. Concerning the pernicious-like anemias of pregnancy Kühnel believes the most important etiologic factor to be the repetition of pregnancy with too short an interval between. This is the explanation for the greater commonness of such severe anemias in multiparæ.

**Treatment.**—The physiologic anemia of pregnancy when it remains within bounds is usually moderate and seems to require little or no treatment, but more serious trouble can probably be avoided by a prompt recognition that anemia is increasing. At such a time the administration of iron, and perhaps the use of liver extract should be sufficient, in the absence of any complication of the pregnancy, to prevent further anemia. Under certain conditions one should be especially on the watch for an aggravation of the usually mild anemia of pregnancy. These conditions appear to be: (a) Previous tendency to anemia; (b)

presence of syphilis; (c) a very short interval between the present and a preceding pregnancy; (d) presence of a pyogenic infection such as pyelitis.

Once anemia is found to be severe, more active measures are perhaps indicated. The French school, following Aubertin, seems agreed that prompt termination of the pregnancy offers the only hope of stopping the anemia. Offergeld claims that the appearance of megaloblasts is a clear indication to terminate the pregnancy. Larrabee's experience would seem to suggest that transfusion will permit the pregnancy to proceed to term.

What effect active treatment of syphilis would have on the anemia in those cases in which this infection is present is difficult to say. No satisfactory report is at hand. It is interesting in this connection to remember the fact so emphasized by Stokes that pregnancy has so beneficial an effect on syphilis as almost to be considered a part of its treatment.

Some evidence is at hand to suggest that help will also be had from the Murphy-Minot diet which is so successful in true Addisonian anemia. Murdoch quotes such a result in a patient postpartum, and Devraigne and Laennec<sup>1</sup> attribute marked improvement to the diet in a case of severe anemia of pregnancy. Even should such result be obtained with ease in the severe anemias of pregnancy, one should be unwilling to conclude from this that the severe anemias of pregnancy are truly "pernicious" in the Addisonian sense.

**Conclusions.**—1. A mild anemia occurs physiologically in pregnancy.

2. This physiologic anemia of pregnancy may become severe in individuals previously anemic or as a result of unusual hemorrhage or of complicating infections, of which syphilis is apparently the most important.

3. Severe so-called pernicious anemia of pregnancy is not identical with Addisonian anemia (primary pernicious anemia). The grade of anemia may be as marked and certain features of the blood-picture suggestive, but other essential criteria are lacking.

<sup>1</sup> Bull. d. l. Soc. d. Obst. ed. Gyn., 1928, 17, 213.

4. Sepsis may be the cause of such an anemia and the lack of leukocytosis does not exclude this possibility.

5. Early recognition of anemia beyond the "physiologic" grade, and prompt treatment will in the majority of instances avoid the development of the severer grades of anemia which in the past have been termed "the pernicious anemias of pregnancy."





# CLINIC OF DR. MARTIN E. REHFUSS

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## CLINICAL LECTURE ON HYPERACIDITY

HYPERACIDITY is a term loosely used and it seems to me poorly defined. This term must not be confused with the subjective symptom of acidity of which many individuals complain. Heartburn and acidity are subjective symptoms which are found even when the stomach is distinctly subacid or anacid. Furthermore, the normal stomach tolerates acid figures which all clinicians agree are equivalent to that grade which is commonly known as hyperacidity. The ordinary "acidity" or "heartburn" of the patient belongs to a group of sensory phenomena and may or may not be associated with high acid figures. It certainly has no place in the understanding of true hyperacidity as revealed by gastric analysis. I believe that the term "hyperacidity" should be restricted to the actual demonstration of acid figures higher than normal encountered during a certain phase of digestion. We know that the optimum or highest acidity is encountered during the height of active gastric digestion. We also know that the fasting secretion, which is ordinarily found between the digestive periods or in the so-called fasting stomach, is appreciably lower in its acid titration figures as compared with the digestive interval. It has always seemed to me that when the figures of the fasting secretion approach those of the digestive secretion, we then have undoubtedly a form of hyperacidity. This is seen in many clinical conditions in which the duodenum is involved, but normally the figures in the first half-hour of digestion and the last half to three-quarters of one hour are comparatively lower than those found during the height of the digestive response. If these two periods show acid figures out of all

proportion to the normal response, they might likewise be construed as forms of hyperacidity. The clinician is familiar with the fact that there are terms for these various types of increased acidity. Fasting hypersecretion and hyperacidity are familiar to all of us. The larval type of hyperacidity is that encountered in the first period of the digestive response, usually within the first half-hour or more. A true digestive hyperacidity is one in which the height of the response is remarked by excessively high acid figures. Postdigestive hyperacidity is one which marks the termination of the digestive cycle or its transit into the interdigestive period. In any event it is conceivable that the response may be abnormal in any particular phase, and my own experience demonstrates that all these forms of hyperacidity can be encountered in disease.

Another phase of the hyperacidity angle is obviously due to the type of food which is used in determining gastric secretion. For years the majority of test-meals have been of the carbohydrate character. The familiar Ewald meal is the typical example of this type, as is gruel, rice toast, and crackers, all of which have been used experimentally in the determination of the secretory activity of the stomach. We have pointed out the fact that the stomach does not respond either from a motor angle or a secretory angle in a similar manner to the various foods. There is no question whatsoever that vegetables and cereals produce a lower acid output whether measured by the  $pH$  of the gastric juice or by titration methods. In 75 observations on breads and cereals the average high total acidity encountered was 80. This included all varieties of breads and cereals. In 124 observations on vegetables the average highest acidity encountered was 75. These figures can be taken as practically standard figures for the behavior of the stomach in health. On the other hand, meats respond in a very different fashion. Beef and beef products reveal an average highest total acidity of 120, and in 14 observations of lamb in normal human beings the highest total acidity encountered in terms of cubic centimeters 10/N alkali necessary to neutralize 100 c.c. of gastric juice, was 135. In 20 observations on the digestion of

chicken the average highest total acidity recorded was 120. In 75 complete observations on the digestion of various types of fish the average highest acidity recorded was 130. In other words, in animal proteins the acid response was very much greater than it was with carbohydrates. In fact, it might be said that in health the normal response to beef, chicken, or even fish is that which is commonly accepted by clinicians as figures illustrative of hyperacidity. The thought immediately occurs that an individual may react with normal figures so far as an Ewald meal or gruel is concerned, but the same individual will show very much higher figures if the meat meal is given. More recently Marcell and I published a communication on "The Gastric Digestion of Meat in Health and Disease." We studied a series of chronically diseased individuals, most of them having conditions other than gastric, both with an Ewald meal and a meat meal. We found that the diseased patient, as exemplified in chronic cardiac, renal, blood disease, and other conditions commonly met with in medical ward service, showed impaired gastric digestion to the meat meal. The amount of meat used in these experiments, however, was only 60 gm. instead of the 100-gm. portions which were used in the original experiments. There is evidence to prove that a 100-gm. portion of meat will give rise to a more complete and higher acid response than 60-gm. portions. The same thing is true regarding the quantities of milk. We found higher acidity with large quantities of milk than with smaller quantities of milk. For instance, 400 c.c. of cows' milk will give an average total acidity of 100, while 75 c.c. will give an appreciably lower figure. In chronically diseased individuals where there are presumably some disturbances in the secretory output, the highest total acidity recorded with a meat meal in 25 patients was 66.5, while the highest total acidity with an Ewald meal was 40, figures which are appreciably lower in both instances than are encountered in the ordinary cross-section of normal human beings. The point which I wish to emphasize is the fact that figures which are normal for carbohydrates are not normal for the response to animal proteins. Furthermore, the figures obtained after the

ingestion of meat, for instance, in normal individuals are commonly those which we have been taught to believe are due to hyperacidity. The inference from these observations is the fact that high acid figures with a carbohydrate meal do indicate a condition which might be called hyperacidity. In other words, if we stick to the carbohydrate meal as a standard for acidity, there are unquestionably cases where a demonstrable increase in acid output may occur in any or all of the phases of digestion. This, to my mind, is a true form of hyperacidity. In our studies on diseased individuals it was interesting to note in various disease conditions that the response to the meat meal was perceptibly greater than the carbohydrate meal. In advanced disease of the mucous membrane, however, such as in pulmonary tuberculosis, in some gall-bladder cases, in chronic gastritis, and also curiously enough in pernicious anemia, the difference in the response to the carbohydrate and the meat meals was not perceptible or very much less. For instance, in the true pernicious anemia the meat meal and the carbohydrate meal both failed to register any perceptible secretory output, while in advanced disease of the mucous membrane the increased stimulus of meat may bring about a slightly higher acid output, but it does not begin to approximate that which is found in health.

The evidence which was accumulated within recent years indicates that the acidity of the contaminated gastric juice tends to become remarkably constant and decidedly greater than the analysis of the gastric contents as they have been secured for diagnostic purposes would lead us to believe. Certainly the concentration of the acid in the native secretion exceeds 0.2 per cent. HCl, that which is usually quoted as typical of the gastric contents. The pure gastric juice is now recognized as attaining at least twice this concentration. When the figures are lower than that, they are not necessarily due to an impaired or perverted secretory function, but rather due to a neutralizing effect of other substances. There is no question, for instance, that the food in the stomach can perceptibly reduce the amount of acidity. Ever since Boldyreff enunciated the idea that the pancreatic secretion could play an important rôle in the control and regulation

of the gastric secretion, it has been apparent that this subject is one of extreme importance. In comparing the alkalinity of the various body-fluids which come in contact with the stomach, it is apparent that there is a very great difference in the availability of these various substances. Expressed in alkalinity in percentage  $\text{Na}_2\text{CO}_3$ , saliva is 0.08 (Neumeister); the gastric mucus, 0.05–0.1 (Boldyreff); the pyloric juice, 0.05 (Shemyakiw); the Brunner's juice, 0.12 (Ponomaroff); the succus entericus, 0.02–0.05 (Shepovalniskoff); the bile from the gall-bladder, according to Boldyreff shows an alkalinity of 0.05; the blood according to Poopkin shows an alkalinity of 0.27, while the pancreatic secretion, out of all proportion to these various substances which have already been quoted, shows an alkalinity which is equivalent to 0.65. It is, therefore, apparent that the alkalinity

TABLE I.—COMPARATIVE ALKALINITY OF THE BODY FLUIDS.

	Alkalinity in per cent. $\text{Na}_2\text{CO}_3$ .	Authors.
Saliva . . . . .	0.08	Neumeister (35).
Gastric mucus . . . . .	0.05–0.1	My own observation.
Pyloric juice . . . . .	0.05	Shemyakin (36).
Brunner's juice . . . . .	0.12	Ponomaryoff (37).
Succus entericus . . . . .	0.02–0.05	Shepovalniskoff (38).
Bile from the gall-bladder . . . . .	0.05	My own observation.
Pancreatic juice . . . . .	0.65	Walter (39).
Blood . . . . .	0.27	Poopkin (40).

(From Boldyreff.)

of the pancreatic secretion is the one outstanding factor which can perceptibly alter the acid content of the stomach. That this is so is proved from a large series of experiments. There seems to be little doubt whatsoever that the regurgitation of the alkaline duodenal secretion is the dominating factor in controlling the acidity of the gastric contents. Not only did Boldyreff show that large amounts of free acid introduced into the stomach rarely ever attained a similar concentration when they were passed into the duodenum, but by a series of experiments on dogs he showed clearly that the free acid as it approached the duodenum was very much less. In the inclosed diagram, for instance, is such an experiment, showing the difference between the free acid introduced into the stomach and the free acid which

is found in the duodenum. Spencer, Meyer, Rehfuß and Hawk, in a study of this same phenomenon, pointed out some time ago by means of the estimation of the trypsin in the gastric contents, according to the method of Spencer, that the reduction in the gastric acidity was synchronous with the increase in trypsin, which was the only satisfactory substance we could investigate as an indication of pancreatic regurgitation. Not only did we demonstrate this mechanism in the normal individual, but Bolden and Goodhart in England, by measuring the chlorids of the gastric contents, were able to demonstrate in a similar way that the acidity of the gastric juice was in a large measure due not only to the acidity of the native secretion but also to the

TABLE II.

(0.5 per cent. HCl run into dog's stomach; A and B, 200 c.c.; C, 300 c.c.)

Time. Intervals 15 minutes.	In the stomach.			In the duodenum.		
	Free acid in per cent. HCl.			Free acid in per cent. HCl.		
	A.	B.	C.	A.	B.	C.
15 min. . . . .	0.38	0.38	0.38	0.13	0.09	Alkaline reaction
Another 15 min. . . . .	0.35	0.33	0.29	0.07	0.14	0.12
" 15 " . . . . .	0.29	0.27	0.22	0.05	0.08	0.08
" 15 " . . . . .	0.25	0.22	0.17	0.03	0.06	0.07
" 15 " . . . . .	0.24	0.19	0.14	...	0.04	0.05
" 15 " . . . . .	...	0.17	0.13	...	0.03	0.06
" 15 " . . . . .	...	...	0.12	...	...	...

(From Boldyreff.)

degree of duodenal regurgitation. In other words, the acidity at any given interval will largely be determined by these two factors. In a more recent report by Olch and Elman, these authors consider the importance of the duodenal contents and believe that regurgitation of this alkaline fluid into the stomach undoubtedly plays a significant part in regulating the reaction in the upper part of the small bowel. As these investigators point out, the acid gastric juice at the concentration in which it is secreted will not be tolerated by the sensitive duodenal mucous membrane. On the other hand, the alkaline pancreatic secretion is then secreted and this fluid goes into the stomach to decrease gastric acidity and lower it sufficiently to be acceptable

to the duodenum. They point out that the reaction of the gastric contents at any time is the resultant of the secretion plus the

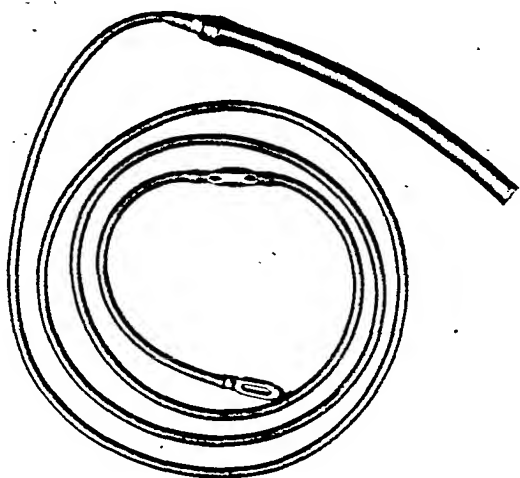


Fig. 163.—Gastropyloroduodenal tube used by author and Dr. Eads in the study of the effect of the pylorus on gastric acidity.

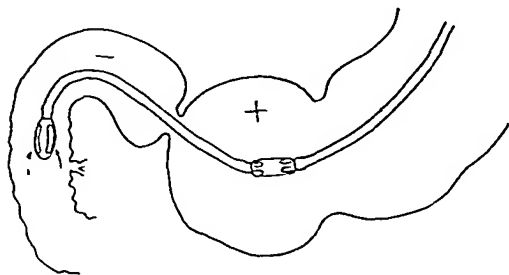
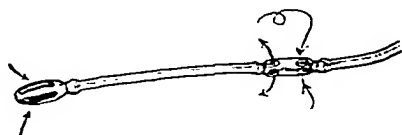


Fig. 164.—Position of gastropyloroduodenal tube.

amount of regurgitation, a factor which I have emphasized for a number of years. It is also interesting to note that the portion



of the upper digestive tract including the prepylorus, pylorus, and duodenum may be regarded as a single organ or mixing chamber where the acid material is prepared for the intestine, and it is in this region where most of the gastroduodenal lesions occur. This problem seemed to me of such importance that I was particularly anxious to approach it from a somewhat dif-

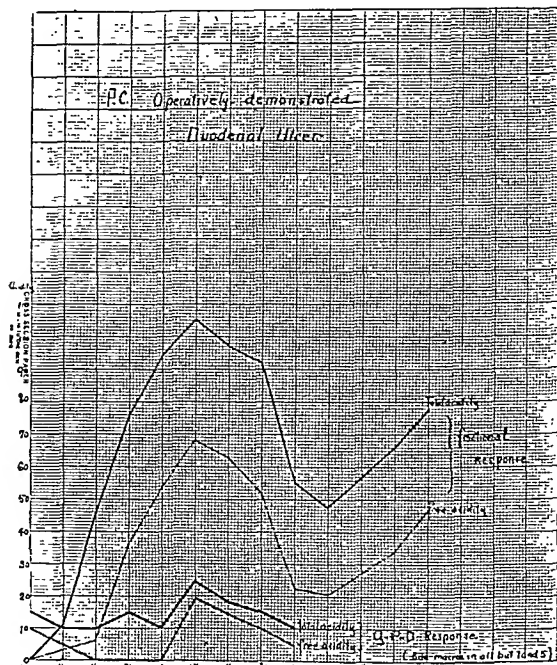


Fig. 165.—Acidity curves in a case of operatively demonstrated duodenal ulcer with a simple carbohydrate meal, and again with the same meal and the gastropyloroduodenal tube.

ferent angle. For this purpose I devised a gastropyloroduodenal tube, the illustration of which is appended. This tube consists of two separate metal pieces. The terminal tip of the tube is the ordinary type of gastroduodenal tube such as was described a number of years ago. At a distance of 4 to 6 inches above this point a second metal insertion is placed, which is perforated at both ends, but solid in the middle. The first terminus is obviously

openly connected with the tip at the end of the tube. The upper perforations of the second metal piece serve as an accessory stomach-tube. The purpose of this gastropyloroduodenal tube is to maintain a patulous pylorus during the period of observation. In other words, the tube is placed into the duodenum and stomach by means of the fluoroscope. This is absolutely essential. The tip of the tube is placed in the second portion of the

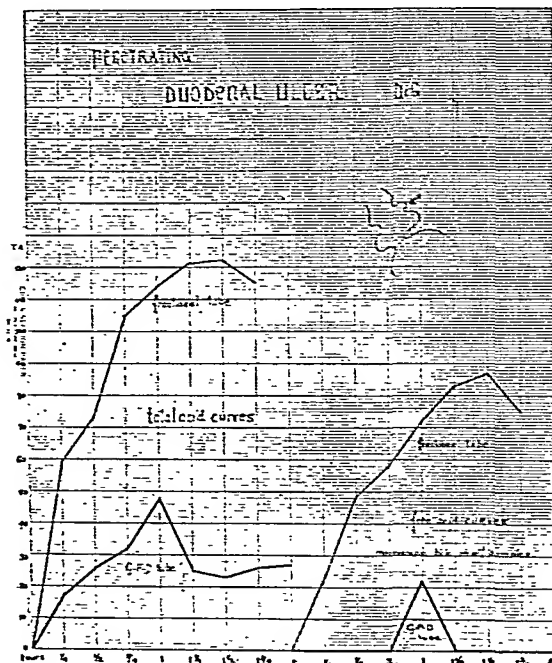


Fig. 166.—Total acid curves in penetrating duodenal ulcer before and after permanent pyloric intubation. Free acid curves from the same case.

duodenum if possible, and the upper metal piece should be well seated in the antrum of the stomach. Observations made with an Ewald test-meal, and then with the same meal with this tube in place, show rather surprising findings. In the appended illustrations are several cases which are of interest. One is a case of operatively demonstrated duodenal ulcer with gastric hyperacidity. The first response is the ordinary one obtained

with an Ewald meal with the tube at or near the gastric antrum. The second response is that obtained with the gastropyloro-duodenal tube in place. Not only is the acid in both free and total curves very much less, but there is evidence of active regurgitation through the entire period. This is shown by the macroscopic presence of bile in practically all the samples. In Dr. S's case of penetrating duodenal ulcer a comparison of total acid and free acid curves is seen, and again the same phenomenon was encountered in a similar series of cases of demonstrated hyperacidity. A certain proportion of these showed unquestionably that it was possible by permanent intubation of the pylorus to markedly reduce the curve. In other words, a method is offered by which the increase in tonus of the pylorus can be overcome. At the regular meeting of the American Gastro-enterological Association, Dr. Eads and I presented a series of cases in which we used this tube. In a certain proportion of these cases we were able to cut the hyperacid curve in half. This was not true in all cases, and the explanation is probable that in some instances the tonus of the stomach as a whole is insufficiently great to prevent regurgitation from the duodenum into the stomach. The fact, however, that in a certain proportion of cases of hyperacidity it is possible to keep the pylorus open and by encouraging regurgitation materially reduce the resultant acid curve, suggests that there is a mechanism at or near the pylorus responsible for a certain number of these cases of hyperacidity. This experimental work has only begun, but the findings are sufficiently encouraging to warrant the belief that the motor mechanism and the sphincteric control are of great importance in this problem. There is scarcely any question that the only available substance capable of reducing a high acid output is the pancreatic secretion. It is also very probable that many of the forms of true hyperacidity are due to lesions at or near the duodenum. It may be recalled in this connection that in 72 per cent. of operatively demonstrated duodenal ulcers Moynihan demonstrated hyperacidity in these cases. In 100 cases of duodenal ulcer I was able to demonstrate high acid figures which I believe to be abnormal with an Ewald

meal in 78 per cent. This is out of all proportion to any group of normal responses and stands as a definite diagnostic fact. It is my belief, however, that any lesion at or near the pylorus that increases the tonus of the pylorus can produce hyperacidity in this way, providing the mucous membrane of the stomach is efficient. There are many factors which come to mind which have to do with the functional efficiency of the pylorus. These factors are now being investigated, and it is altogether probable that within the next few years we may have a more definite explanation regarding the exact control of the secretory mechanism.

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# CLINIC OF DR. EDWARD A. STRECKER

## JEFFERSON MEDICAL COLLEGE

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### THE TOXIC MENTAL REACTIONS

I AM presenting for your consideration a number of patients who are or have been mentally disturbed by reason of the influence of either exogenous or endogenous toxins. Since you will see many such instances these cases are given only a brief presentation, so that enough time will remain to clarify your ideas. No detailed attempt will be made to authenticate the diagnoses of the organic diseases from which these patients are suffering. In each instance the diagnosis rests on definite physical and laboratory signs and has been well established.

#### PRESENTATION OF PATIENTS

Case I.—This adult male patient has lobar pneumonia. He has a fever of 103° F., pulse 120, respirations 45. The lower and middle lobes of the right lung are consolidated.

When he was admitted one week ago his speech was rambling and irrelevant or he was busily engaged in conducting imaginary conversations. His illness had not been recognized and he wandered out of the house in his night-clothes.

Now you see that he is answering "voices." We were able to determine that he believes he is in Spain and thinks that he is talking with his son who is really dead. Frequently he is apprehensive and extremely restless and active.

Case II.—This young woman gave birth to a male child one week ago. She has fever and the uterus may be palpated half-way between the umbilicus and the symphysis. An examination revealed that placental fragments had been retained.

Occasionally this patient realizes she is in a hospital, but usually she is confused and disoriented. There has been active hallucinosis—the Virgin Mary, faces staring at her, angels with harps, etc. For a short time she believed that the baby was to be killed.

**Case III.**—This boy has severe osteomyelitis of the left humerus. He is very talkative and violent. Sometimes he tears up the bed-sheets and attacks other patients. He speaks of "ether," "electrical waves," etc. People call him "bad names" and pinch his arm. He sees angels with halos about their heads and sometimes God addresses him. Often he is dazed and confused.

**Case IV.**—This young man has delirium tremens. He has been drinking steadily for three weeks and averaged a quart of whisky daily. He is restless and apprehensive. The marked feature of his delirium is the fearful hallucinosis—snakes, cats, dogs, pigeons, "small animals" crawl over the bed-sheets and over his skin. In terror he strikes out at lions, tigers, snakes, dogs, pigeons, mice, rats, and alligators, or frantically brushes away imaginary insects.

**Case V.**—The next patient is a baker who was overcome by illuminating gas from a defective gas-stove. Two weeks after the accident he became fatigued and dazed. Then he apparently thought he was working in the bakery, since he mixed up whatever he could find as though he were kneading dough. He has not been extremely active, but merely restless, and his behavior reveals that he feels he is engaged in his daily work. This is spoken of as an occupational delirium.

**Case VI.**—The last patient, a woman forty-two years old, is addicted to morphin. She states that she began to take the drug several years ago, in order to overcome the pain of neuralgia. The average dose is 7 to 8 grains daily. There are no mental symptoms at this time, but she is irritable and complains of great fatigue. There have been episodes during which it was necessary to send her to an institution. At these times she was noisy and fault-finding, accuses her family of conspiring to cause her pain and of trying to kill her. She saw horrible faces and the pictures on the wall waved back and forth so that she could not sleep.

## DISCUSSION

As the first and more formal portion of this clinical course proceeds, you will realize that there is some justification for a division of abnormal mental reactions into three great groups: the organic, the toxic, and the functional.

The organic group includes those types of mental reactions which may be more or less directly traced to actual tissue changes or pathology in the brain. In this connection you will immediately think of paresis, in which disease the cyto-architecture of the brain is disarranged and destroyed by the invasion of the Spirochæte. The senile and arteriosclerotic psychoses constitute somewhat similar examples.

In dealing with the third group, it is advisable to state that the designation "functional" is a confession of ignorance. It simply implies that in the present state of our knowledge we have not been able to discover significant pathological, chemical, or metabolic alterations. We assume, therefore, that the psychiatric phenomena are the expression of psychologic maladjustments. This may or may not be true. Hysteria and, perhaps, dementia præcox or schizophrenia are fair illustrations of "functional" disturbances.

The second group, or the toxic, is the subject of the few remarks which I am about to make. Here the dynamic factor concerned in the deviation from so-called mental normality seems to be a toxin or poison. This foreign and harmful element may be introduced into the body from without, as in alcoholic-, opium-, or lead-poisoning, or it may be created within the organism as, for instance, in typhoid fever, pneumonia, or uremia.

I should be sorry to give you the impression that there are hard-and-fast demarcations between the organic, functional, and toxic psychiatric reactions. Often the boundaries are vague and sometimes they vanish. Frequently, even in such a well-defined organic psychosis as paresis, we may witness the operation of toxic and "functional" influences. Again, in a febrile delirium it is sometimes possible to trace in the mental symptoms the characteristics of the individual personality. Finally, in dementia præcox, there is a wealth of both organic and toxic clinical material. When we speak of organic, toxic, or "functional" psychiatric reactions we merely express the implication that the major part of the clinical picture suggests the predominance of one or the other of these conceptions.

#### TOXIC MENTAL REACTIONS AND INTERNAL MEDICINE

There is no group of mental reactions more important to the medical student and practitioner than the toxic psychoses. Considered from a broad standpoint, it is clear that in this field there is no division or demarcation between internal medicine and psychiatry. In one sense psychiatry is not a specialty of medicine, *it is medicine*.



It may be put concretely. Let us assume that as practitioners of medicine you are treating a patient who has lobar pneumonia. The case is simple and uncomplicated. There are the usual reactions of fever, consolidation of the lung, changes in the circulation, etc. Everything is quite definite and obvious. Then, perhaps in a short time, two or three hours, the picture changes suddenly and completely. Either as a result of the fever or the toxins, or both, the physical signs retreat into the background, and the patient shows striking mental symptoms—confusion, disorientation, restlessness, and hallucinosis. Here is a clear illustration of the fact that there is no real line of separation between internal medicine and psychiatry.

You must realize that in any physical disease, infection, cardiac disease, metabolic disorder, or what you like may be abruptly transformed into mental disease. Unless you do realize this, you will be at a very serious loss and will find yourself inadequate in the conduct of your practice.

In other words, you must anticipate that in the course of any physical disease such phenomena as disturbance or loss of consciousness, hyperactivity, hallucinosis, and other symptoms may appear. You will be nonplussed unless you have in mind that these symptoms are simply a part of and a continuation of the same condition, which a few days ago was a simple uncomplicated case of lobar pneumonia, typhoid fever, myocarditis, or what not.

The theme might be continued indefinitely. It should be obvious from a consideration of the toxic psychiatric reactions and from the mental aspects of physical disease that internal medicine and psychiatry are so intimately related that they really belong to each other.

From what has been said, it must be obvious that the toxic psychiatric reactions must be extraordinarily common. In this respect statistics from mental hospitals are misleading. Including those of alcoholic origin, the rate would be placed at less than 10 per cent. The discrepancy is clearly explained by the fact that the majority of those who are mentally ill on a toxic basis are never admitted to public mental hospitals. They are

treated in general hospitals, in small private institutions, in the home, and as ambulatory clinic and office patients. These toxic manifestations are so numerous as responses to a great diversity of exogenous and endogenous poisonings that it is impossible in a single lecture to attempt to describe them individually. Fortunately the chief features are held in common and there is a diagnostic pattern which to some extent holds true in all instances. What then are the characteristics of these abnormal mental reactions?

### ETIOLOGY

One of the cardinal and distinguishing traits of these psychoses is *the definite etiology*. Here we may expect to cover a wide range, but usually the cause is ascertainable. It may be strictly exogenous, and in this connection we would naturally consider alcohol, opium and its derivatives, and the entire class of hypnotic and narcotic drugs, the metals and gases used in the industries, etc. When we turn our attention to endogenous agents, we think at once of the host of acute infectious diseases such as typhoid fever, influenza, and pneumonia. Here the mental equilibrium may be upset by the fever primarily or by the toxin. Usually both are operative. Then we must reckon with the effect of more chronic infections, notably tuberculosis. Heart disease, particularly in the stage of decompensation, exerts a decided influence on mental functioning. Again, there are a whole series of chemical alterations, blood dyscrasias, metabolic disturbances and deprivations and endocrine imbalances, which are expressed not solely in terms of organic dysfunctions, but often and sometimes predominantly as psychic disorders. One might continue indefinitely, but perhaps the frequency, variety, and tangible etiology have all been sufficiently stressed.

### PHYSICAL INDEX

The second important and common aspect is the physical index. It is well to remember that the physical phenomena such as fever or coated tongue are as much a part of the whole picture as is the mental confusion or the hallucinosis. It is not necessary to recount the somatic manifestations of fever, toxicity,

or exhaustion. They are variable in severity, but all in all they are distinctive. Here are embraced fever, pulse alterations, vasomotor and sympathetic signs, headache, pain, nausea, vomiting, constipation, loss of weight, and many other symptoms. In addition, there are the findings more peculiar to the underlying pathologic state, whether it be tuberculosis, pneumonia, heart disease, pernicious anemia, exophthalmic goiter, uremia, carcinoma, or what not. You will at once realize that the sum total of physical findings may be amplified and greatly extended by the information which is contributed by the various laboratories—clinical, chemical, x-ray, serologic, and the like. If scientific methods and resources were more constantly utilized, then the percentage of psychiatric reactions in which the responsible exogenous or endogenous agent remains undiscovered would be enormously reduced.

#### THE MENTAL PATTERN

The third point concerns the possibility of tracing a fairly accurate mental pattern. While it is true that this pattern shows considerable variation not only by reason of the degree of severity of the toxicity or exhaustion but also according to the personal make-up of the sick individual, yet it is somewhat consistent. It seems to me that the essence of the toxic reaction type is delirium. It is important for you to understand what is included in the symptom-complex called delirium.

Delirium implies some amount of clouding of the consciousness. The contact between the individual and his real environment has been broken or at least it is impaired and insecure. He is no longer keenly aware or is not aware at all of the happenings in the environment. In other words, the personal, temporal, and spatial relations, one or all, have become weakened or even severed. The patient is disoriented.

Hallucinosiis is apt to be a component of delirium. At one end of the scale may be placed the extreme and vivid hallucinatory content of delirium tremens; at the other the occasional, mild, and transitory hallucinatory content of moderate fever.

In any event, unfounded sensory impressions constitute a prominent detail of the picture.

To complete the triad of symptoms there is motor restlessness. It may be mild or severe; general in its type or special. There may be slight motor unrest; uncontrolled, wild, and seemingly purposeless activity, or the movements may be specialized, in that the patient seems to be carrying out some occupation—the baker mixing his dough, the tailor threading his needle.

At this point perhaps it is worth while emphasizing that in psychiatry nothing is really purposeless. Especially is this true in the non-degenerating psychoses. Be the behavior and speech ever so bizarre, illogic, and impenetrable to the observer, yet it has a meaning in the inner mental life of the patient. I remember a woman who for months frantically clawed at the walls of her room until she had dislodged large sheets of plaster. The whole performance seemed inexplicable and a sign of dementia. With recovery came, too, explanation that the patient had believed herself a prisoner in a submarine at the bottom of the sea.

If you now have in mind that the widest latitude in the severity of symptoms is to be expected, then there will not be very much difficulty in recognizing the clinical syndrome which expresses bodily toxicity. On the basis of the delirium with its disturbance of consciousness, hallucinosis, and motor overactivity there may be added marked affective lability, perplexity and apprehension, irrelevant and incoherent speech, transient delusions often with a persecutory trend, varied illusions, catatonic phenomena, stupor, and many other manifestations.

**Resistance.**—The question of resistance is highly interesting. I know a boy who becomes hazy and confused whenever his temperature mounts to 100° F. On the other hand, a famous lawyer recently became infected by enteric fever. He had two relapses, hemorrhage, peritonitis, polyneuritis, and other complications. In spite of these serious and repeated physical insults his mind remained relatively clear. Several weeks after all the typhoid symptoms had subsided he suddenly became confused, active, suspicious, hallucinated, violent, and homicidal. This exhaustion reaction continued for many weeks. To offer

an explanation for the varying amount of individual resistance which must be broken through before fever, toxicity, and exhaustion can upset the mental balance is very difficult. "Inherent instability of the nervous system" is merely a formula of words. It is important, however, to realize that resistance is not a fixed quantity or of a standardized quality. It may be said that it is never exactly the same in any two individuals, nor even the same in any single individual at two different periods of his life. In a general way the strength or weakness of resistance is dependent on everything that has gone before—hereditary influences, and personal, somatic, psychologic, and environmental stress and strain. Theoretically at least everyone has a toxic, febrile, and exhaustion mental threshold, and when that threshold is reached then there will be psychotic phenomena.

#### PROGNOSIS

The final point which toxic psychiatric reactions have in common is the prognosis. This is a very practical point for the medical man. The prognosis is in a very large percentage of cases quite good. In other words, we are in a field of psychiatry and internal medicine in which the great majority of patients experience complete restoration to mental health.

Usually the recovery is a fairly rapid one, so that within a few weeks to a few months the patient is well. Occasionally, however, we meet remarkably protracted cases. I knew a woman who was admitted to a mental hospital following the birth of her third child. She at that time had septic endocarditis and septicemia, and developed a toxic psychosis. It was diagnosed dementia præcox. She was in a mental hospital for seventeen years. For five years she did not utter a single intelligent word. For three years she took no food voluntarily and had to be artificially fed. She was regarded as demented and entirely hopeless.

One day one of the members of the staff who was more curious than the other members came across this patient. He sat down and asked her some questions, and to his great surprise she answered freely and intelligently. He examined her several

times and, finally, he concluded that she was perfectly well, normal, and sane in every way. That patient was discharged from the hospital and lived the remainder of her life in excellent mental health. It is the longest duration of a toxic psychosis ever reported.

So even after years the outlook in these cases may be good. The practical lesson is that one should never be willing to discontinue the effort to restore the mind to health.

### TREATMENT

The treatment of toxicity from the standpoint of psychiatry teaches an extremely logical and practical lesson which should be carried over into internal medicine. It is simple and obvious therapy, but it is life saving. It rests on the principle of removing the toxin from the body as rapidly as possible. The keynote is elimination. The constant temptation which must be resisted is the employment of narcotic drugs. The physician must not permit his judgment to be weakened by the fact that the patient is noisy and the environment is disturbed. It is the patient who is to be treated and not the environment. To introduce an added toxin into a body which needs every ounce of resistance and eliminatory capacity is illôgical and often destructive to life.

In two groups of delirium tremens patients the mortality rate was 20 per cent. higher in the first group receiving hypnotic and narcotic medication than in the second, made up of the same number of patients, who were placed on a strict régime of liberal fluid intake, very free elimination and hydrotherapy, without resort to sleep-producing drugs. It may be repeated and emphasized that fluid intake and output from the various avenues of the body, in other words, dilution and elimination, should be the first consideration in the therapy of the toxic psychiatric reactions.

In the treatment of a given case it may be necessary to tap every resource of modern medicine. In addition to the general measures which have been indicated there is often the need of intravenous infusion and hypodermoclysis, colonic irrigation, routine dietetic and tonic treatment. It may be necessary to

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direct special attention to chronic constipation. There should be a careful search for and judicious removal of all actual foci of infection. Surgery, sera, vaccines, the x-ray, and radium all have their field of usefulness. The underlying somatic disease, whether it be typhoid fever, malaria, pellagra, heart disease, myxedema, or what not, must be vigorously combated. A major consideration is the preventive aspect, but this may be conveniently discussed after a brief review of the exogenous toxic psychoses.

### EXOGENOUS TOXIC MENTAL REACTIONS

It is historical that at all times the human animal has more or less deliberately taken poisons into the body. A long time ago the native burden bearer in the forests of South America discovered that he could ease his labors by chewing the leaves of the coca tree. In Africa the betel-nut is utilized. In China and many other parts of the world the smoking of opium is practised. Effete civilization drinks tea, coffee, cocktails, whisky and synthetic gin, and smokes cigarettes. All these and many other substances are poisons. Almost every human being has a minor vice. A Professor of Pathology used to remark: "Lord, help the man who has no bad habits. When he gets sick, he has nothing to give up." This may have been a defense reaction.

As early as the year 185 B. C. Lysander discussed the drink prepared from the tears which exude from the head of the poppy. Opium has been known for many hundreds of years. Pliny described opium suicides. In 1729 a great Chinese emperor, Yung Cheng, promulgated an edict against the smoking of opium. Almost two hundred years elapsed before this measure received the support and sanction of a modern, civilized government. Cocain was introduced into medicine much later than morphin. It is the drug of the underworld.

### PERSONALITY OF THE DRUG ADDICT

There has been a great deal said about the personality of the drug addict. The ordinary conception is that he is a weakling, a psychopathic inferior, a notorious liar. It is assumed that he is

unfit to associate with other men. It is difficult to decide just how much of this is intrinsic in the individual, how much results from the drug taking, and how much is due to the fact, that like the sex pervert, the habitué faces a world which does not understand and has "thumbs down" on his case. In many instances the undesirable traits appear to be in relation to the problem of securing the drug. When he is faced by this problem he may become an enemy of organized society; sometimes a ruthless enemy. Naturally, in the advanced and hopeless drug victim, there is produced a so-called ethical deterioration. It is the result of many years of addiction and is comparable to the physical decay by which it is accompanied.

It is true that frequently even the confirmed and chronic drug user retains some shadow of a desire to be free of his habit. At the same time he is unable to bear the thought of being deprived of the staff on which he leans so heavily. Thus, we may witness a curious, two-sided mental reaction, as though one-half of the mind sought relief, while the other half continues to take thought against that day when the drug supply would be cut off.

Often this psychologic quirk is illustrated by the individual patient. A woman comes to a physician and on bended knees begs to be cured of the habit of taking morphin! It is alienating the affection and respect of her husband and children, and her life is being ruined. She is willing to promise anything; to cooperate in every way. In good faith the physician sends her to a hospital. That same evening he is informed that when the patient's clothing was examined it was discovered that several hundred morphin pellets had been sewed into the hem of an undergarment.

#### WITHDRAWAL SYMPTOMS

When such a drug as opium or its derivatives is suddenly taken from an habituated individual then we may expect the development of certain withdrawal phenomena. If none of these signs occur in the patient who is undergoing treatment, then the assumption must be that access to the drug has not been successfully closed. The symptoms of withdrawal are many and

varied. We may anticipate at least a few of the following: Restlessness, insomnia, frequent yawning and sneezing, a feeling of oppression especially in the chest, involuntary movements of the hands, arms, and legs, cardiac palpitation, marked fatigue and weakness, sweating, pain, severe agitation, and sometimes delirium and death.

Naturally, I cannot cover the wide range of the symptomatology of the exogenous poisons. Alcohol produces an astounding variety of psychiatric reactions—delirium tremens, acute and chronic hallucinosis, more or less chronic delusional states, Korsakoff's psychosis, alcoholic pseudoparesis.

The ultimate effect of long-continued poisoning by a potent exogenous toxic substance is nearly always the same. The entire mental fiber deteriorates and, finally, there is a permanent blunting or loss of one or more of the faculties of the mind. Capacity, judgment, attention, memory, moral sense, and the like are impaired or lost. Dementia closes the scene.

A word should be said about the very wide-spread and indiscriminate use of the so-called "harmless" drugs like bromids, veronal, luminal, and the like. They have their proper use, but too often they are abused. There are no restrictions on their sale. It is the commonest thing in the world to suggest to someone who has a restless night that he take a mild hypnotic. Certainly this is a deplorable practice. Probably the majority of those who act on such loose advice are not seriously harmed, but there is undoubtedly a residuum, beginning in this way and finally taking more dangerous toxins to their physical detriment and unhappiness. In reality there are no "harmless" drugs and even the mildest hypnotic may eventuate in a toxic psychiatric reaction.

#### PREVENTION

Prevention is practical and promising. In respect to somatic disease and in the industrial poisons the situation is obvious. In the first instance the prevention of disease, its skilful management after it has occurred and sufficiently long periods of convalescence are requisite; in the second, rigid insistence on cleanliness and hygiene will prove tremendously effective.

The problem of the prevention of alcohol, opium, cocain, and other intoxications is not so simple. There are probably between 1,500,000 and 2,000,000 drug addicts in the United States. No one would venture to give statistics concerning alcoholism. It is an American tendency to salve the national conscience by making a law. Such antilaws are placed on the statute books in great numbers. Some of them are good and operate effectively; many of them are utterly worthless. Perhaps it would be a better plan to study the problem scientifically and when actual information has been obtained, it may be made the basis of calm, dispassionate, and non-hysterical propaganda.



## CLINIC OF DR. JAMES E. TALLEY

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#### OPTIMISM IN PROGNOSIS IN CARDIOVASCULAR DISEASE

MOST of us have had at some time a patient who starts his history by saying: "Twenty years ago Dr. A. told me that I had a grave heart condition and that I ought to take life easier. Now Dr. A. has been gone fifteen years and here I am. Fifteen years ago Dr. B. told me the same thing, but he has been gone five years and here I am." As to whether his former doctors were pessimists or precisionists, it is hard to say. The latter are so anxious to give an accurate prognosis that they overlook the fact that individuals do not always conform to actuarial expectancy nor to the theory of probability in the particular disease group to which they belong. We will run over the histories of a few patients who are still alive and yet should not be if they were not exceptions to the general rule.

Case I.—The first patient was admitted to the Presbyterian Hospital 5/17/19, complaining of dyspnea and lower abdominal distress. About two weeks before admission while engaged in the arduous task of felling a tree, he was seized with pain in the back and went to bed for four days. On getting up, he noted dizziness, dyspnea, and a keen sense of distress in the abdomen—all especially marked on exertion. About this time he also had swooning sensations, occurring several times a day and especially frequent after eating. The day before entering the hospital during one of his attacks he lost consciousness for a few seconds. The patient was a man of sixty, 71 inches tall, and weighing 153½ pounds. He was an artist by profession, but often gets his exercise by chopping or using other tools. He had typhoid fever fifteen years before and many years ago had a cellulitis surrounding a wound in the leg; otherwise he has always been well and hearty. The only tobacco used was three or four pipefuls a day. The slight precordial distress and dyspnea disappeared shortly after entering the hospital. There was no edema and no palpitation.

The heart was apparently normal in size, the sounds were poor, no murmurs were demonstrated, occasionally there were dropped beats or inefficient premature beats; the former seem more likely, but so soft were the heart-sounds that it was practically impossible to tell with a stethoscope over the apex whether an inefficient premature beat was present or not. The apex-rate during his stay in the hospital varied from day to day and sometimes from almost hour to hour. The lowest rate was 32, the highest rate while recumbent was 76, and on rising at the end of a week, it ran up to 80. It often was in the forties and occasionally in the sixties, but as long as the patient was recumbent, he experienced no cerebral disturbance during the passage from partial to complete block and the reverse. His blood-pressure during this stay was 105/50. His lungs were clear of râles; his liver was palpable and there was some pulsation. The urine averaged: acid, specific gravity 1.012 to 1.026, albumin negative, sugar negative, microscopic negative. The Wassermann was negative. The blood-count on admission was hemoglobin 65 per cent.; red blood-cells, 4,580,000; leukocytes, 9450. The phenol-sulphonaphthalein output showed the first hour 87 c.c., 20 per cent.; the second hour 48 c.c., 15 per cent.; thus, the total was 35 per cent. for the two hours. x-Ray examination showed the heart was normal in size and there was no aneurysm. When the patient reached the hospital on the 17th, the rate at the apex was 34, but by the time the first electrocardiogram was taken it had risen to 60, and later in the day it was as low again as 48. This first electrocardiogram showed only slight prolongation of conduction, a left preponderance, and P-3 and T-3 inverted.

The patient remained in the hospital until 5/26/19. He left feeling fairly well except on exertion; he no longer experienced vertigo on rising from a chair or going upstairs as he did before coming to the hospital; his pulse was now 80. He was to return home with the understanding that if the pulse fell to 40 or below, he would come back again immediately. A month later the patient reports that he has gained 2 pounds. He retires from 9 to 10 and remains until 11 o'clock the following day. He realizes that during the night his heart often misses beats, but he has a feeling that his heart is getting stronger; he can walk better, and often is able to forget that he has a heart. Today he walked one-quarter of a mile to catch his train without any discomfort; meeting many people and talking with them disturbs him more than a little exercise. He no longer has any abdominal distress; has no vertigo, no dyspnea, and he feels that his heart responds to exercise. Today after walking a few squares, the pulse was 88; after sitting it fell to 80; the blood-pressure was 110/68. The patient went along fairly well during the following months, but in March, 1920 he began to have vertigo and fainting fits again. On March 8, 1920 the electrocardiogram showed distinctly 2 to 1 heart-block; the auricles were running at the rate of 85, and the ventricles at 42.5; the apex-rate just before the electrocardiogram was taken was 40. On April 12, 1920 he began having a succession of fainting spells though quiet in bed; during this time the condition appeared desperate and it was only by the co-operation of the patient that his life was spared. He stayed in bed for three months and it was during this time that the condition passed into permanent block. Since the block has been

permanent he has had comparatively little trouble. The fact that the patient during this stay in bed of three months taught himself to read French with facility is an index of his resourcefulness in a trying period. Following this transition the patient improved and was able gradually to take up his usual occupation, so that I did not see him until May 27, 1921. He then weighed 154½ pounds, his apex-rate was 28 and regular, he reports that he sleeps most comfortably on his right side, turned partly on the face; he arises at 11 o'clock, he can walk at the rate of 2 miles an hour for any length of time, but the rate of three miles gives him distress at once. He has had no fainting spells for a year; his blood-pressure now is 140/65; the electrocardiogram shows complete block and there is no evidence of left preponderance in these curves, the urine is normal; he still finds that emotional disturbance upsets his heart more than work. In January, 1926 the radial and the apex were both 36 and regular, just after walking three blocks; he has not counted it himself for a long time, but a local physician recently found it 35. He walks to the postoffice, four miles distant, and paddles a canoe. He had just finished crating 12 pictures, tearing up old cases and rebuilding new ones without help. He can do almost anything except hurry. Violent quick exercise tires him and brings on dyspnea. If he walks fast in the dark he is conscious of a flash of light before the eyes at each heart-beat. His blood-pressure is 130/50. Urine is normal. The heart still shows no enlargement; apex 36 and regular, and there is a muffled systolic murmur at the apex which appears negligible. 10/19/26: He is remarkably well, leads an active life, and his avocation is building a 25 foot sloop. At present he still has the same evidences of complete block as revealed by physical examination and an occasional electrocardiogram. He apparently carries on as comfortably as he did in 1926. His willingness to stay recumbent for three months during the severe attack of 1920 until complete block was thoroughly established was the thing which saved his life. During that time one would have been justified in prophesying a demise in almost any attack. All the remedies advised and used under similar conditions were used without any marked influence. He is the only patient in my experience who weathered so many attacks of equal severity.

*Summary.*—Here is a man with severe Stokes-Adams syndrome, due to the passage from incomplete to complete block and the reverse, over several months. During all this time his life was in jeopardy. Fortunately, when complete block was thoroughly established, he had no more trouble. His attacks of cerebral anemia were entirely due to the passage from one degree of block to the other and not to those sudden falls in ventricular rate which we find in many cases, and which have an even graver outlook. He is leading a comfortable and fairly active life nine years after his original attack.

*Case II.*—The second patient was fifty-eight years old when she was seen first in 1912. She was already developing Heberden's nodes which were tender. She had cramps in the legs at night and had several attacks of pleurodynia and stiffness in the neck muscles. At this time she had a well-developed mitral systolic murmur with no enlargement of the heart. Her previous infection was tonsillitis and her tonsils were removed two years



later. She had diphtheria at twenty-one years. The patient was seen again in 1916. She was conscious of premature beats—the apex-rate was 68, the systolic pressure was 132/74; in addition to the mitral systolic murmur there was also now heard an aortic systolic murmur, but no diastolic. Her sleep was poor, and she had had two spells in which she felt she was about to lose consciousness. In 1921, due to over-exertion during the hot weather, she was conscious of the heart again. There was the throbbing under exertion, the blood-pressure was 150/90, and there were the same murmurs as before. The urine was always negative. At this time there were ventricular premature beats of which she was conscious and she found that she had to give up her brisk gait or become conscious of her heart. It was late in 1921 when right branch-bundle block was first found. About this time she began to complain of pain in the precordium and left shoulder, with some degree of pain down the left arm and even the left leg. In spite of this new evidence of myocardial change she went about as usual, going to California and Honolulu. Repeated electrocardiographs showed that right branch-bundle block still persisted. Her blood-pressure was now 150/85; as long as she realizes her restrictions and rests an hour or more a day she has a comfortable life. At times she has pain in the left shoulder and arm, face, and head, but they are not as severe as the average angina, although they are relieved by nitroglycerin. In October, 1927 the patient reported that she had kept about during these years as before; she has a little more dyspnea and palpitation, there is occasional precordial pain, radiating to the left wrist, sharp but not persistent. Her heart is not markedly enlarged, the rhythm is regular, the aortic second is markedly accentuated, and there is the same systolic murmurs at the aortic cartilage and the apex. Her pulse, standing, was 88, sitting 64. Her blood-pressure was 122/66; her vessels are rather hard, and the electrocardiogram still showed right branch-bundle block. Her doctor recently reported no marked changes in her condition.

*Summary.*—Here is a woman of seventy-four with marked cardiovascular sclerosis, dilatation of the aorta, recurring heart pangs radiating to the arms and a right branch-bundle block existing for seven years, and yet she lives a fairly comfortable and active life. The branch-bundle block is especially important as an index of wide-spread myocardial degeneration. It is not unlikely that the patient was a hypertensive case before she came under our observation.

**Case III.**—The third patient, an artist, was forty-four years of age when first seen in 1900. His past infections were tonsillitis, typhoid fever, pleurisy, and probably scarlet fever. In 1904 he had apparently an acute eczema; in 1910 he complained of pain in the right shoulder, and in 1914 apparently had a left-sided kidney colic. He had recurring rashes on the hands and face which it was thought might be due to pigments and a solution that he often used. In 1916 his heart was found normal, his blood-pressure 160/88, his tonsils large and unhealthy looking, and he again had pain in his left shoulder and feet, with erythematous spots suggesting erythema nodosum. In 1921, when he was sixty-five years old, his angina pectoris began. In July of that year he experienced marked precordial pain on exertion, begin-

ning in the pectoral muscles and extending to the left arm and fingers. He had it continually until December, when he said that he still had pain every day if he moved about at all, that it was a little less severe but more frequent than it had been the preceding months. In February, 1922 any exertion precipitated the pain, it had the same distribution, but occasionally it appeared also on the right side. By this time it was worse when he first began to walk, but it gradually grew somewhat better. During the summer of this year, although he had the pain, it apparently was somewhat better. By the autumn, however, he had bad dreams, was startled in his sleep, partly no doubt because he had been reading up on the subject of angina pectoris. Early in 1923 walking even a square slowly gave him marked pain in the left axilla, left scapula, left arm, and fingers. The pain stops as soon as he remains quiet. He recently had a phlebitis in his right leg without temperature; this kept him quiet and during that time he was entirely free from pain. Later in that same year he complained of pain in both arms, more severe in the left wrist and back of the left hand, recurring every day that he goes outdoors. Again, in the summer of 1923, although he had pains they appeared to be less severe as long as he restricted his gait. During 1924 the pains were about the same. In 1925 during the summer he was freer from pain, but he noticed it was provoked by the cool, early morning, mountain air. But, again, it improved after walking a bit. By the autumn of that year the attacks were just as severe as ever. Walking to a bathroom, or lacing his shoes, or even getting out of bed, provokes the pain. It is substernal, across the chest, to the shoulders, down both arms, and especially bad in the left wrist. Belching relieves it somewhat, as it always has. Recent x-ray of the gall-bladder with dye showed that it contained no stones and functioned normally. During the last three years the pain recurs if he moves rapidly or gets excited; in fact, he is never free from it except when quiet, but it is not as intense as it was before. His blood-pressure, taken many times during these years, was never higher than the one recorded in 1916, but there was a gradual shading off from the 140/85, which was the average pressure up until 1924, to a pressure of 104/68 in 1928. The electrocardiograms which have been taken on many occasions have always shown slight prolongation of conduction, but no other evidence of myocardial or coronary involvement and the polygrams show no alternation. The attacks of pain and the distribution have been so characteristic of angina pectoris that there seems little doubt of the diagnosis. The continuous prolongation of conduction in all electrocardiograms, the small voltage, the lessened blood-pressure and the soft sounds of the heart all point to a continuous lessening of cardiac efficiency. The attacks have been continuous since they began in 1921, but are perhaps less intense now than they were originally. Two explanations occur: one is the condition of the patient himself from time to time—physical tire, emotional disturbance, flatulence, and unfavorable weather conditions—all impress these patients strongly. Again, although the electrocardiograms suggest no occlusion of an important coronary vessel, the recent injection of the coronary arteries followed by roentgenograms setting forth the circulation of the heart have given us new insight into the cardiac circulation. Many of the smaller coronary branches show variations in diameter and

sometimes fusiform aneurysms without any complete occlusion. In response to this, on one hand, it is conceivable that anastomoses have taken up the work; just as, on the other hand, we know that fibrotic replacement of good muscle-tissue often takes place.

*Summary.*—Here, then, is a man who has had a syndrome of angina pectoris since 1921. For long intervals the slightest movement produced disabling pain, and he has rarely been free from some degree of pain on exertion during all this time. Yet, just at present, I am sure he is more comfortable than he was formerly.

**Case IV.**—The fourth patient, a woman of fifty-six, was admitted to the private floor of the Presbyterian Hospital on December 3, 1926 and discharged in January, 1927. She had auricular fibrillation, subnormal temperature, an average blood-pressure of 130/68; she had generalized edema with effusion in both pleural cavities. The patient had had abnormal heart action for two and one-half years. In April, 1926 she had an operation for adenoma of the thyroid and made a good recovery. The following June she started from bed suddenly in fright, had heart-consciousness more than ever after this; just afterward she developed pneumonia and was sick for several weeks. Early in October of the same year she had a serious attack of urticaria, "affecting not only the skin but also the larynx." Since the pneumonia she has had edematous legs and recently some swelling of the abdomen. Just before the admission the kidney excretion was 7 ounces per night. After admission the urine was usually acid, specific gravity 1.020 or above, albumin a trace, sugar negative; at first there were hyaline casts and later, hyaline and light granular. The electrocardiogram showed auricular fibrillation, blood-sugar was 90 mg. per 100 c.c., blood-urea nitrogen was 17 mg. per 100 c.c. The blood-count was practically normal, and the differential count was normal. On admission, heart-rate was 80, and the radial 50. A pulse deficit of 30. On the first day after admission, under digitalis and theobromin sodium salicylate, the urine jumped from 10 to 76 ounces, the fluid being restricted to 1000 c.c. Examination of patient on admission, 12/3/26, showed short rapid respiration, flatness over both lungs well above the angle of the scapula due to effusion, the heart somewhat large and very irregular, marked ascites, the legs markedly edematous; by December 7th the patient was irrational at night. This irrational condition and finally a semicomatose condition persisted until early in January, so that the patient's mind was a blank as to that period. As following a single dose of novasurol there were some red corpuscles in the urine, it was discontinued, and Niemeyer's pill was given. The pulse deficit continued until the 19th, when coupled beats began to appear. At this time the left chest especially was clearing. Again, on December 20th, novasurol was given once more, with good results. By the 22d the right chest was free, the ankles were better, but the left effusion persisted. Several days later the pulse deficit was reduced to four. On January 3d the patient was rational, and the edema largely subsided. She was discharged on January 17th, the edema having entirely disappeared. Some three months later she had another attack of beginning edema, but under digitalis and theobromin sodium salicylate it disappeared.

Again, in November, 1927, she had edema of the legs, but it disappeared with prompt treatment. She reported just recently, May, 1928: she is still fibrillating, but the rate is 76, she has no edema, the urine is normal, and she leads a fairly comfortable life.

*Summary.*—A woman past middle life with auricular fibrillation due to a toxic adenoma, who had both pleural cavities filled with fluid, whose ascites was marked and general anasarca extreme, whose urine suggested a nephritis, and who was comatose, certainly did not suggest a promising outcome. A heart that responded to digitalis and kidneys that were capable of stimulation pulled her through.

*Case V.*—The fifth patient, a woman past sixty in 1920, had a sudden weakness and numbness in the left side, the left arm becoming distinctly paretic; her tongue was thick. She was seen for the first time some three months later; at that time she had a systolic pressure of 210 and a diastolic of 120. The urine at that time was acid, had a specific gravity of 1.011, showed a trace of albumin, no sugar, and the microscopic examination was negative. The phenolsulphonephthalein elimination was 55 per cent. She was rapidly recovering, and soon after this the weakness of the arm entirely disappeared. The blood-pressure has been taken dozens of times in the last eight years, the systolic varies from 175, but is more often 200, and on various occasions it has risen as high as 240. The diastolic pressure is usually about 100, 105 would be an average, but it often runs as high as 120, and occasionally it has gone up to 130-140. She has a heart that is enlarged, electrocardiograms always show left preponderance and occasionally a premature beat. Polygrams have never shown alternation. From time to time she has complained of a thumping heart, marked buzzing in the head, and awakes frightened in the night, but she has never complained of the typical headaches of the hypertensive type. In 1924 her ophthalmologist reported: "A typical sunburst deposit, such as we see in chronic interstitial nephritis. I could not find any evidence of retinal hemorrhages. This type of retinitis albuminuria is usually the forerunner of retinal hemorrhages, so that her eyes should be watched for this condition, but it may not take place if the blood-pressure is kept down." At this time her blood-urea nitrogen was 16 mg. per 100 c.c.; the urine has never had a low and fixed specific gravity through all these years; it has usually contained a trace of albumin, sometimes a cloud, but then it always contains some leukocytes. Hyaline casts are usually to be found, but granular casts are rare. They were reported about the time of the ophthalmologist's report, but afterward they disappeared and did not again occur in the numerous reports which we have had since. Recently her blood-urea nitrogen was 17 mg. There has been no recent report from the ophthalmologist, but there has not been any complaint on the part of the patient, so that in all probability she has not developed any retinal hemorrhages. Since 1922 examinations of the nervous system have been entirely negative, and one could not detect any weakness of the left hand and arm.

*Summary.*—A patient past sixty of a hypertensive family and herself suffering from hypertensive cardiovascular disease developed weakness of

the left side and especially of the left arm eight years ago. This was probably due to a so-called vasomotor crisis or what was known earlier as a serous apoplexy. The gloomy forebodings of those who saw her in the initial attack have not been fulfilled. She has led a fairly quiet life, but has been abroad once, is able to go about everywhere, and walks considerable, and yet she has not had any semblance of a new attack of palsy.

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### TACHYCARDIA AND HYPERTHYROIDISM. REPORT OF THREE CASES WITHOUT EVIDENT ENLARGEMENT OF THE THYROID GLAND OR EXOPHTHALMUS

RAPID heart action in a patient with enlargement of the thyroid gland or associated with exophthalmus does not present any difficulty in diagnosis. Simple tachycardia is the term used to describe ordinary rapid heart action, with a rate ranging from 110 to 160 per minute in the adult, and results from excitement of the accelerator nerves of the heart.

It occurs in many conditions and may be functional or organic in origin. In a number of individuals the heart-rate varies normally between 90 and 100 per minute.

Exercise, fright, over-exertion, fever, and disorders of the heart are among the commoner causes of simple tachycardia. In gastro-intestinal conditions tachycardia frequently is present. Tachycardia is a prominent symptom in hyperthyroidism and the neuroses, and can result from the excessive use of tea, coffee, or tobacco. A clinical entity which is classified under the neuroses, namely, neurocirculatory asthenia or effort syndrome, frequently presents difficulties in diagnosis, especially if it occurs in young adults with some enlargement of the thyroid gland.

Case I.—Mr. R. D., aged fifty-five years, was seen October 23, 1926, complaining of rapid heart action, restlessness, weakness, 20 pounds loss in weight, regardless of an excellent appetite, and attacks of unexplained frequent bowel movements—four to six daily. These symptoms had gradually developed over a period of six months. For the past three months the patient was unable to follow his occupation as an architect because of his poor state of health. His physician advised him to take a rest at the seashore. Instead of being benefited by rest and the bromids his condition gradually became worse.

The past history was unimportant except that in childhood he suffered a severe attack of scarlet fever. During the year previous to the onset of his present illness he had some unpleasant business relations with several of his important clients, causing him considerable worry, to which he attributed his decline in health.

The physical examination revealed a well-developed adult who showed evidence of weight loss. No exophthalmus was present. The thyroid gland was not palpable. The lungs were clear and resonant throughout. The left border of the heart extended 13.5 cm. to the left of midsternal line in the fifth interspace and 2 cm. to the right in the fourth interspace. A presystolic thrill and a double mitral murmur were present. The systolic element was transmitted to the axilla. The liver, spleen, and kidneys were not palpable. The patellar reflexes were exaggerated. Pretibial edema was not present. The skin was soft, warm, and velvety to the touch. The pulse was regular, and the rate 112 per minute. The temperature was 99.1° F. at 3 P. M., the blood-pressure 120/80, and the weight 119 pounds. The basal metabolism performed the next morning (after a preliminary test the previous afternoon) showed a rate of +37. During the test the radial pulse-rate, which was regular, increased from 120 to 136 and became irregular, due to the development of auricular fibrillation. The fractional gastric analysis (twenty-minute intervals for a two hour and forty minute period) showed an increase in total acid and free hydrochloric, the former ranging from 30 to 110 and the latter from 22 to 78. The maximum figures were obtained at the end of two hours. Roentgen-ray examination of the chest showed an increase in the transverse measurement of the heart, but no evidence of pulmonary tuberculosis or substernal goiter. The blood-Wassermann was negative and the blood-count showed a slight secondary anemia.

**Discussion.**—In order to recognize the condition responsible for the tachycardia we must consider as possible etiologic factors organic heart disease, an infection such as pulmonary tuberculosis, a neurosis, a gastro-intestinal disturbance, and hyperthyroidism.

The mitral-valve signs indicate that organic heart disease was present, and it is most probable that the damage resulted from an attack of endocarditis during the illness caused by scarlet fever. If disease of the myocardium had been responsible for the symptoms complained of, one would expect that with a heart-rate varying from 110 to 120 per minute for a period of several months, other signs and symptoms of congestive heart-failure would be present, such as dyspnea on effort, cough, râles at the bases of the lungs, an enlarged liver, ascites, and pretibial edema. The absence of these findings and a normal electro-

cardiogram were considered sufficient evidence to rule out organic disease of the heart as being responsible for the symptoms complained of. The auricular fibrillation present during the basal metabolic test was temporary, and disappeared within an hour after the test without any treatment excepting that the patient remained in bed. It must be admitted that the heart of this patient is not normal, but that the diseased condition has not progressed sufficiently to account for the illness of the patient.

A cardiac neurosis, commonly referred to as effort-syndrome, neurocirculatory asthenia, or irritable heart, has as a prominent symptom tachycardia. The skin of a patient with this type of neurosis frequently shows evidences of the vasomotor instability, such as mottling, or a cold and clammy condition. The skin of our patient was warm, moist, and velvety, and did not present the changes seen in a neurosis. Loss of weight in the presence of excellent appetite is not a common finding in neuroses. The basal metabolic rate in an uncomplicated neurosis is normal. We have noted frequently in effort-syndrome that while the basal metabolic rate was being determined the pulse-rate decreased and even returned to normal. This was not the case in this patient, whose pulse-rate during the test became more rapid with the development of auricular fibrillation which continued for an hour.

The pulse-rate in a cardiac neurosis is usually variable and may fluctuate within a wide range, especially upon excitement or effort. The pulse-rate during sleep usually returns to normal. The pulse-rate of our patient remained continuously elevated during the day and night. Upon these findings we eliminated effort-syndrome as the cause of the patient's symptoms. The tachycardia, weight-loss, and afternoon rise in temperature suggest pulmonary tuberculosis as a possible underlying cause of the patient's condition. The absence of physical signs in the lungs, the patient's age, and a negative history of tuberculosis, and Roentgen-ray examination of the chest are sufficient data to eliminate pulmonary tuberculosis as the etiologic factor responsible for the symptoms complained of by the patient.



Gastro-intestinal disturbances are frequently accompanied by rapid weight loss, tachycardia, and frequent bowel movements. Physical examination did not disclose any tender points in the abdomen. The patient enjoyed an excellent appetite and did not complain of any symptoms referable to the gastro-intestinal tract except frequent, formed bowel movements. The high gastric acidity is not a common finding in organic lesions of the stomach (notably cancer), which are associated with rapid weight loss and frequent bowel movements. The absence of sufficient symptomatology and physical signs to account for the condition of the patient to be ascribed to a gastro-intestinal lesion warrants the elimination of the gastro-intestinal tract as the etiologic factor in the condition of the patient.

If this patient had showed evidences of goiter one should have readily made the diagnosis of hyperthyroidism. The rapid pulse-rate, the loss in weight, excellent appetite, the increased basal metabolic rate, the slight rise in temperature, the soft velvety skin, the fibrillation of the auricles under excitement, nervous irritability, and hyperacidity of the stomach contents with frequent bowel movements strongly suggest overactivity of the thyroid gland, which was the diagnosis made. Exophthalmus, accompanied by these symptoms and no enlargement of the thyroid gland, also occurs, but in this patient there were no signs of enlargement of the thyroid or exophthalmus.

Before coming under our care he had been taking 12 minims of tincture of digitalis three times a day and ascribed his over-active bowels to the digitalis medication.

**Treatment and Progress.**—The patient was ordered to bed beginning November 1, 1926.

A diet rich in carbohydrates and fat with meat or two eggs (once daily) was ordered. Milk was allowed freely.

Ten minims of Lugol's solution three times daily were given and a record of the weight, the temperature, and the pulse was kept. At the end of two weeks very little improvement had resulted, so the patient was given a series of Roentgen-ray treatments. The beginning of the fourth week the patient's pulse-rate began to lessen, and the weight to increase. On

December 2, 1926 the pulse-rate was 88 per minute. By December 23, 1926 the patient had gained 15 pounds, now weighing 134 pounds, and the pulse-rate continued to be 88 per minute.

From this date the patient gradually improved and remained in bed until February 25, 1927. His weight at this time was 138 pounds, the pulse-rate 76 per minute, and the basal metabolic rate +2. Between this date and May 1, 1927 his weight varied between 138 and 140 pounds and his pulse-rate from 72 to 80 per minute. On the latter date he returned to his work on half time and soon thereafter on full time and continues to date to be symptom free. The patient made a slow but good recovery of his normal state of health upon treatment for hyperthyroidism.

Case II.—Mrs. S. B., age thirty-nine years, after a strenuous season of social activities, in February, 1926, noticed almost constant palpitation of the heart, began to lose weight regardless of an excellent appetite, was restless and irritable. She recognized that she tolerated warmth very poorly. Her strength failed, and the sleep was frequently disturbed. The bowels moved frequently without a laxative, a condition never before present. Bromids and rest were prescribed, but she did not improve. Her menstrual history was negative. She has never been pregnant.

Examination made May 15, 1928 revealed a moderately well-developed woman. She was restless and her skin highly flushed. The eyes showed nothing worthy of note. The neck did not show enlargement of the thyroid gland or any undue pulsation of the blood-vessels. The lungs were clear and resonant throughout. The left border of cardiac dullness extended to the midclavicular line in the fifth interspace. The sounds occurred regularly, were of good muscular tone, and no murmurs were heard. The abdomen was normal in outline and the liver, spleen, and kidneys could not be palpated. The patellar reflexes were exaggerated. The skin was warm, moist, smooth, and velvety. The temperature was 98° F., the pulse-rate was 120 per minute, and the blood-pressure 120/80. The blood-count was hemoglobin 88 per cent., the red blood-cells 4,500,000, and the white blood-cells 7200. The examination of the urine was normal. The blood-Wassermann was negative. On account of the tachycardia an electrocardiogram was made which showed nothing abnormal. Basal metabolic rates made on three different days averaged +29. Roentgen-ray examination of the chest was negative for substernal goiter or disease of its contents.

Comment.—Except for the absence of the enlargement of the thyroid gland and exophthalmus the classical symptoms and signs of hyperthyroidism were present, and treatment for

this condition was begun. The patient had been treated for nervousness and the therapy consisted of bromids to an ambulatory patient who was gradually becoming worse. When the cause of her illness was recognized to be overactivity of the thyroid gland she was treated by absolute rest in bed and an ice-collar to the neck for a period of eight hours daily. Lugol's solution was given in 5-minim doses three times daily for five days to note if it would be tolerated. Subsequently the patient received 10 minims Lugol's solution with  $\frac{1}{2}$  grain luminal three times daily. At the end of two weeks the Lugol's solution was discontinued for a week and its administration resumed for two-week periods with intervals of one week during the course of seven weeks.

A basal metabolic test was performed every ten days and at the end of seven weeks it was  $+12$ . The patient was allowed to return to her home, continuing the rest in bed during the afternoons and the Lugol's solution.

During her seven-weeks' stay in the hospital the patient was given a liberal diet, except for meats and eggs, which were allowed in quantities not to exceed 150 gm. of meat and two eggs daily. Before she left the hospital she regained 15 of her 20 pounds and her pulse-rate ranged from 70 to 76 per minute and the symptoms had almost entirely disappeared. Her skin continued to have its warm, smooth, velvety texture and often appeared flushed. This did not exist prior to the present illness. During the previous summer and autumn she noticed the roughness of her skin, caused by her outdoor life, disappearing. The change in the texture of the skin is frequently an early sign of hyperthyroidism.

Because of her improvement on rest and drug therapy she was not given Roentgen-ray treatment.

The tachycardia with slight variation in rate in any twenty-four-hour period and with loss in weight and strength, an increased appetite, frequent bowel movements, and a characteristic skin and finally an increased basal metabolic rate which gradually returned to normal, proved our diagnosis of hyperthyroidism to be correct.

We believe that this patient must continue her rest and in the future avoid conditions that will cause great strains on her nervous system to prevent the possibility of a recurrence of her condition.

Case III.—S. B., a man aged forty-eight years who for thirty years had worked in the office of a paint factory, came under observation October 9, 1926, complaining of tachycardia, weakness, and a loss in weight of 34 pounds during the past year. The patient's general health was excellent until fifteen years ago. In 1911, from April until December, he was absent from his work complaining of palpitation, loss in weight and strength, nausea and vomiting. The diagnosis made at that time was a nervous breakdown and he believes the symptoms of his present illness are similar to those of his previous illness. Although he made a good recovery in 1911 he never was capable of making the same physical effort as previous to his illness. He lacks endurance, and physical effort induces palpitation of the heart.

In November, 1925 he suffered an attack of grip which confined him to the house for three weeks. He did not recover his previous state of health as rapidly as he felt he should, and in June, 1926, upon the recommendation of his physician, he consulted a dentist, who found several abscessed teeth and extracted them. The examination of the urine at this time showed the presence of 1.5 per cent. of sugar. The blood-sugar percentage was not determined. A diagnosis of diabetes mellitus was made because of the excellent appetite, the loss of weight and strength, and the glycosuria. From July until October, 1926, he was on a weighed diet. Upon the diet without the use of insulin the urine was either sugar free or contained less than 0.5 per cent. Although his glycosuria seemed under control the patient states he was not making any progress. He was brought to the hospital by automobile, being unable to walk more than the length of an ordinary sized room without resting.

In addition to the symptoms described and the history, the patient states that he has not been under any unusual physical or mental strain, and considered that his health was better than any time in the previous ten years until he suffered this attack of grip. He did not use tea, coffee, or alcohol. His appetite was excellent, and his bowels moved normally each day. His family history has no bearing on his present condition. He was never overweight. His best weight was 160 pounds, fifteen years ago. There were no symptoms referable to the gastro-intestinal or respiratory tract. He was nervous and irritable due to the failure to retard the decline in his state of health.

**Physical Examination.**—The patient showed evidence of weight loss and appeared very weak. It was an effort for him to speak. There was no dyspnea or cyanosis present. Exophthalmus was not present.

The pupils reacted normally to light and accommodation.

The tonsils had been removed and the oral hygiene was good. The neck was thin and the veins were prominent. The thyroid gland was not enlarged. The pulsation of the arteries in the neck was very noticeable and occurred irregularly. The chest was symmetrical in outline. The lungs were clear and resonant throughout. No râles were heard. The apex-beat of the heart was diffuse, occurred irregularly, and was palpated in the fifth and sixth left interspaces outside the midclavicular line. No shocks or thrills were present. The left border of cardiac dulness extended 13.5 cm. to the left of the midsternal line and 3.5 cm. to right midsternal line in the fourth interspace. A soft systolic murmur transmitted to the axilla was present in the mitral area. The sounds occurred rapidly though irregularly and approximated a rate of 100 per minute. There was no pulse deficit.

The liver was not palpable. The pulsation of the abdominal aorta was very evident. Ascites was not present. The patellar reflexes were normal. There was a coarse tremor of the extended hand with spread fingers, more of the character of one due to weakness than to hyperthyroidism.

No pretibial edema or clubbing of the fingers was present. The skin was warm, smooth, and velvety to the touch. The blood-Wassermann was negative. The Roentgen-ray examination of the chest was negative except for the presence of an enlarged heart. There was no evidence of intrathoracic goiter. The basal metabolic test taken every other day for three examinations averaged +50.

The urine examination on ordinary diet during the first week of our observation showed less than 0.66 per cent. sugar, and the average output of urine varied from 960 to 1500 c.c. in twenty-four hours. The blood-sugar determined on third day of our observation was 0.93 per cent. A maintenance diet plus 25 per cent. based on 160 pounds weight was instituted and continued for three weeks, the patient being confined to bed. The urine promptly became sugar free and the blood-sugar was 0.90 per cent.

Physiologically assayed tincture of digitalis was given during this three-week period—40 minims every twenty-four hours.

The improvement in the patient's condition was noticeable, his spirits were better, but his heart-rate remained about the same as on admission—100 to 110 per minute and irregular. At this period the patient was given 10 minims Lugol's solution, in addition to the tincture of digitalis, three times daily for a two-week period. The weighed diet was also continued. At the end of one week of iodine therapy the heart-rate decreased to a range of 90 to 100, but the basal metabolic rate continued high (+44). In view of the rest and the digitalis therapy it was our feeling that the patient should have shown greater improvement.

Roentgen-ray treatments to the thyroid gland were inaugurated. Lugol's solution, digitalis, and diet were continued during the course of three weeks. At the end of this period the pulse continued to be irregular, the rate averaged 84 per minute, and the patient had gained 11 pounds. His basal metabolic rate at this time was +28. Two weeks later the patient returned to his home, continuing his treatment, and the diet again was increased 25 per cent. After one month at home the patient had another series of x-ray treatments.

The patient improved gradually and regained his normal state of health within five months after undergoing treatment for hyperthyroidism. The patient has been examined at intervals of six months and his condition found to be as satisfactory as one could expect with the degree of heart disease present. The hyperthyroidism, glycosuria, and tachycardia have been controlled.

Physical examination of the patient in July, 1928 showed the patient engaged in his work, and his state of health about as usual. The thyroid gland is enlarged on the right side due to a small tumor (adenoma). This is the first time a tumor or enlargement of the thyroid has been noted. The heart continues to fibrillate and its rate ranges from 76 to 80 per minute. No signs of congestive heart-failure were present. The weight of the patient was 140 pounds and has been stationary for the past eighteen months. Examinations of the urine by the patient for the presence of sugar have been negative. His appetite con-

tinues to be excellent and he possibly exceeds his food allowance, although he states that sugar does not appear in his urine. He declines to have a blood-sugar determination or a basal metabolism test, both of which usually upset his nervous system.

*Discussion.*—There was some doubt as to the cause of the patient's condition when he first came under observation. Did the patient have diabetes mellitus or was his condition due entirely to the heart disease? Was the glycosuria due to a disturbance of metabolism other than diabetes? The tachycardia could readily be ascribed to the condition of the heart, but the extreme loss in weight and the excellent appetite, the high basal metabolic rate must be due to some other disturbance of function. Diabetes mellitus has a symptomatology similar to that described, but is not usually associated with heart disease at this age unless arteriosclerosis is advanced. Were the condition due to diabetes, the readiness with which the glycosuria disappeared when the patient was put on a weighed diet without the use of insulin should have resulted in more improvement than the patient experienced, especially so when one considers that the blood-sugar was normal. The basal metabolic rate should have declined more rapidly with the institution of proper dietetic control. The lack of adequate response of the heart to the moderately large digitalis dosage suggests an extracardiac cause, in part responsible for the tachycardia.

The basal metabolic rate taken soon after the patient came under observation was +50. While metabolic disturbances such as diabetes mellitus, infections, fever, and exercise are capable of giving increased rates, they seldom rise above +30 except in extreme cases. In the absence of a more favorable response to diet and digitalis, and in the presence of tachycardia, loss of weight and strength, glycosuria, auricular fibrillation, a characteristic smooth velvety skin, and an increased metabolic rate, we concluded that the condition must be due to hyperthyroidism and the results of the treatment verified our conclusions.

Less than two years after the patient came under our observation we noticed for the first time an adenoma. It is possible that this adenoma may have been a factor in the onset of this

condition, but it is also known that acute infections may precipitate overactivity of the thyroid gland in what may be termed a potential hyperthyroid individual. In this case the illness followed an attack of grip. Possibly the patient's symptoms fifteen years previous to the present trouble also had their origin in the thyroid gland.

The condition of the heart of the patient was the result of a toxic thyroid, as no other cause more plausible can be discovered.

The patient, although denying being of the nervous type, is most apprehensive. He undoubtedly should at present have a careful study of his thyroid function, and if the basal metabolic rate is increased, measures should be instituted to control the activity of the gland and prevent further damage to his heart.

#### SUMMARY

Three cases are reported in which tachycardia is an outstanding symptom due to a toxic thyroid gland without evident enlargement. In two of the three cases the tachycardia is associated with a damaged heart, but with no other evidence of congestive heart-failure.

The recognition of the etiology of the tachycardia is rendered difficult because enlargement of the thyroid gland did not accompany the symptoms and other signs of hyperthyroidism. It is important to identify the cause of tachycardia, especially so in hyperthyroidism, because of the importance of instituting early and proper treatment and thereby preventing further damage to the heart.

The occurrence of glycosuria in association with hyperthyroidism reminds one of the similarity in the symptomatology of diabetes mellitus and hyperthyroidism.

The glycosuria of hyperthyroidism has its basis in the disturbance of the function of the thyroid gland, and it is usually controlled when proper measures for the treatment of hyperthyroidism are instituted.

Diabetes mellitus occurring in association with hyperthyroidism must be treated in accordance with accepted standards



regardless of thyroid gland. The glycosuria associated with hyperthyroidism should be kept under observation lest it develop into true diabetic glycosuria.

The future course of these patients will be interesting and, unless carefully controlled and treated, evidences of hyperthyroidism may reappear.

## CLINIC OF DR. HENRY DRAPER JUMP

PHILADELPHIA GENERAL HOSPITAL

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### JAUNDICE. WITH HISTORIES OF NINE TYPICAL CASES

THIS is a fairly common symptom which appears in many disorders. It is so spectacular that the patient is alarmed and seeks advice early. This is fortunate, for it is often the first symptom of a very serious disease. Usually it is easily detected by the marked yellow tint of the skin, mucous membranes, and scleræ; when mild, the scleræ alone may show the tint. In negroes the skin will show a yellow underlying tint by indirect light; the palms of the hands may, but the scleræ always show it. Caution must be used not to be deceived by the natural pigmentation of the orbit in this race.

The discoloration is due to the deposit of bilirubin in the superficies, because of an increased amount in the blood.

The jaundice varies from a very light color, as the grape-fruit hue seen in pernicious anemia, to a deep yellow, or it may even be brownish (bronzed) or greenish. If well defined there is no difficulty in detecting it, but in the milder forms it may be confused with the sallowness of secondary anemia.

The degree of jaundice may be determined by the *icterus index*, obtained by comparing the blood-serum with solutions of bichromate of potash of various strengths. The index will show about 5 for normal serum; when it runs between 5 and 15 it is *latent jaundice* and hard to see; when above 15 the jaundice is well enough marked to be easily seen.

There are two principal varieties of jaundice:

1. **Obstructive**, which is due to some gross obstruction to the outflow of bile, with consequent injury to the liver tissue and

reabsorption of the bile constituents. The stools become putty-colored from the lack of bile-pigments and the urine highly colored from the increased amount in it. Bile-salts as well as pigment are usually found in the urine.

2. **Non-obstructive**, in which there is no evidence of gross obstruction, but in which, ultimately, obstruction is apt to play a part.

While it seems proved that bile-pigment may be formed entirely independently of the liver, the fact remains that even in purely hemolytic jaundice the liver does participate in the formation of the bilirubin. In toxic jaundice at least there is swelling of the liver-cells and engorgement of the vessels which cause obstruction of the biliary capillaries.

Non-obstructive jaundice may be divided into two classes:

(a) **Toxic or infective**, which is due to certain infections and poisons. The cause may be injury to the liver-cells or a cholangitis, which leads to obstruction in the small bile-ducts.

(b) **Hemolytic jaundice**, which is due to disintegrating changes in the blood constituents. The spleen is an important factor in the production of this variety. It is characterized by a higher bilirubin content of the blood, while the urine generally contains none.

The van den Bergh test offers a method for differentiation of obstructive from non-obstructive types. It is the reading of the reaction which occurs between blood-serum and the freshly prepared diazo reagent of Ehrlich. The *indirect* reaction is purely quantitative and determines in units the amount of bilirubin in the blood: it occurs with both types of bilirubin. The *direct* reaction determines the source of the bilirubin and may be immediate, delayed, or biphasic.

*Immediate Reaction*.—Begins within thirty seconds and reaches the maximum color in two to three minutes. It occurs in *obstructive* jaundice.

*Delayed Reaction*.—Begins slowly after thirty seconds and reaches the maximum in thirty minutes or more. It occurs in *non-obstructive* jaundice.

*Biphasic Reaction*.—Begins within thirty seconds and reaches

its maximum slowly, perhaps in one hour. It indicates an obstructive type with a possibility of non-obstructive cause also.

**Obstructive Jaundice.**—The obstruction may affect:

1. The common duct.
2. The hepatic duct.
3. The ducts within the liver substance.

Jaundice does not follow obstruction of the cystic duct, so that in gall-stone colic, for instance, there is no jaundice, however prolonged and severe the pain may be, until the stone passes into the common duct. Then the bile is backed up in the smaller ducts, bilirubin is absorbed, and jaundice follows.

Obstruction may occur *inside* the ducts or from pressure *outside*.

Obstruction *within* the ducts may be due to:

- Gall-stones (most common).
- Foreign bodies and worms from the duodenum.
- Stricture or obliteration from injury.
- Spasm of the ducts (most rare).

Obstruction *outside* the ducts may be due to:

- Tumor of the head of the pancreas (usually carcinoma).
- Tumor of the stomach, duodenum, right kidney, or of distant organs, as the ovary, uterus, or omentum.
- Enlargement of lymph-nodes in the fissure of the liver (syphilis, Hodgkin's disease).

Aneurysm of the hepatic artery or other branches of the celiac axis.

Kinking, as from floating right kidney, or other visceroptoses.

Adhesions due to peptic ulcer, inflammation of the gall-bladder, and perihepatitis.

Pressure on the *smaller ducts within* the liver may be due to:

Pathologic conditions of the liver, as in biliary cirrhosis, abscess, and new growths (cancer, gumma).

Marked congestion of the liver due to cardiac and other diseases which interfere with the circulation (rare).

Toxic or infective jaundice may be due to:

Catarrhal inflammation of the mucous membrane (catarrhal jaundice).

Infectious fevers, as yellow, relapsing, typhoid, typhus, malaria, scarlet fever, pneumonia, and septicemia.

Spirochetal infection (syphilis).

Acute yellow atrophy.

Poisons, as phosphorus, arsenic (inhalation of AsH and intravenous for syphilis), toluylendiamin, chloroform, trinitrotoluène, and dinitrobenzol.

Toxicity of pregnancy.

**Hemolytic Jaundice.**—This includes: Primary anemia (pernicious anemia, Banti's disease, and Gaucher's disease).

Icterus neonatorum.

Familial jaundice.

*Dissociated Jaundice.*—This French term includes those conditions in which either the bilirubin or bile-salt is retained and reabsorbed into the blood, while the other is excreted in the normal way.

In hemolytic jaundice the discoloration depends on bilirubin produced by excessive blood destruction through overactivity of the cells of the reticulo-endothelial system, especially of the spleen. In this condition the excretory power of the liver is, for practical purposes, normal.

Itching, which is frequently observed in obstructive jaundice, is thought to be due to deposit of bile-salts in the skin. It is usually absent in hemolytic jaundice.

With this classification let us proceed to the study of such illustrative cases as are available. These cases, with but one exception, have been taken from the wards of the Philadelphia General Hospital, from my service or that of my colleagues.

The jaundice will usually be plainly evident. One may be deceived by the sallow appearance of one with a wasting disease and consequent secondary anemia. The color of the scleræ will usually determine if jaundice be present. If this does not, the icterus index or the indirect van den Bergh will do so.

Then the van den Bergh will determine almost positively whether it be obstructive or non-obstructive jaundice. Non-

obstructive jaundice ultimately calls for much more systemic disturbance than the obstructive, and the discoloration is less marked. In other words, the jaundice predominates more in obstructive jaundice, and systemic disturbance more in non-obstructive jaundice.

**Case I.**—Obstructive jaundice; gall-stones; possible obstruction from cyst of right kidney.

The patient is an unmarried white woman, sixty-five years old. For several years she has had attacks of mild to severe epigastric pain, with bursting distention of the abdomen when the pain is severe. The pain is radiated to the right shoulder and back; she has vomited but once in these attacks. There have been belching, hunger distress, and other evidences of indigestion during these years. There have been constant stiffness and pain of the back, which were attributed to chronic arthritis of the spine. Within the past few months her back has been injured twice by falls. These have exaggerated the backache, but apparently have not contributed to the present attack of jaundice. There is no history of a previous attack of typhoid fever.

A week ago she had a chill which was followed by headache and severe pain in the epigastrium and both shoulders which lasted several hours. Three days later she had a very bitter taste; then putty-colored, foul stools and dark urine, which stained her clothes, appeared. She then noticed she was jaundiced. None of these symptoms has ever occurred with the previous attacks of pain.

In this case one is probably justified in making a diagnosis of biliary colic with jaundice, due to an obstruction of the common bile-duct because of: (a) Continued indigestion and distending pain; (b) severe epigastric pain with radiation to the shoulders; and (c) jaundice with its associated signs. The examination adds little to the information already gathered.

*Examination.*—The skin and mucous membranes are markedly yellow; the discoloration is particularly noted in the eyeballs. The nurse reports today that the stools show a bit of brown color and that the urine is lighter. The yellow stains on her nightgown are caused by the bile-colored urine.

She shows no evidence of pain nor does she seem seriously sick. There is no embarrassment of respiration, though she states she is dyspneic on exertion; cyanosis and edema of the extremities are not present. She is obese, the trunk is broad, and the costal angle is very obtuse. This combination of constitutional properties is usually found in gall-bladder disease. The heart-sounds are weak and distant; the lungs are negative. The epigastric and right hypochondriac regions are moderately resistant, the gall-bladder region is tender, the liver and gall-bladder cannot be palpated. No masses are felt in the abdomen. The temperature, pulse, and respiration have been normal.

At one time a mass was felt in the region of the right kidney. This was

thought to be a cyst, which pressed upon the common duct and produced jaundice. It has not been felt since. It is hardly likely a cyst could exert enough pressure to cause obstruction with severe pain.

The urine showed a trace of albumin, no casts, sugar once at an early examination, no bile-pigments.

The blood showed a moderate anemia, sugar 111 mg., urea nitrogen 17 mg., cholesterin 170 mg.

The van den Bergh is reported as biphasic and almost immediate. This places the case in the obstructive class.

An x-ray examination revealed no stones or other conditions which would help. This is not an unusual report, for gall-stones frequently (about 50 per cent.) are not sufficiently dense to make a shadow.

The Graham-Cole method gives much better visualization of the gall-bladder. This consists of administering intravenously or orally the sodium salt of tetraiodophenolphthalein. This salt is excreted in the bile and its iodine content causes a shadow.

The test is contraindicated when there is a badly damaged liver. In jaundice there is more or less liver damage, so the test is usually withheld in the presence of jaundice. Graham has used the dye under such conditions with no greater percentage of reaction, but believes it ought not to be done promiscuously.

When we add the tenderness and rigidity in the upper abdomen and note the absence of systemic disturbance and of symptoms pointing elsewhere, the diagnosis previously made is more justified.

In the previous attacks of pain without jaundice it is likely the stone engaged in the cystic duct and fell back into the gall-bladder when the duct distended. In the last one it went into the common duct and thence into the duodenum or remained in the duct which had distended enough for a little bile to flow past. The gall-bladder and common duct should be explored and possible stones removed; but the patient, who is a good surgical risk, declines the operation.

*Later Notes.*—Within three weeks the jaundice entirely disappeared, the urine and stools having resumed their normal some time before.

**Case II.**—Obstructive jaundice from gall-stones—painless at first, sharp pain later; acute pancreatitis.

These notes of a patient, aged forty-eight years, illustrate a peculiar combination of symptoms. "Silent" jaundice is very unusual with gall-stones. In middle-aged persons it excites suspicion of cancer of the head of the pancreas, which is the cause of the obstruction in Case III.

On February 22d the patient fell ill with vague indigestion and nausea, without abdominal pain. The next day he was jaundiced; this gradually deepened and in a day or two dry, foul, colorless stools, dark urine, and marked itching appeared.

As there had been considerable indiscretion in food before this, he was thought to be suffering from catarrhal jaundice despite his age. Bile drainage was done, without good effect. Nausea was persistent with occasional vomiting until March 12th. During the next week the jaundice varied

in intensity, the stools began to show a little brown color, and the patient felt better except for heartburn.

At this time he fell under the care of his family physician, Dr. George A. Knowles, who saw that deep jaundice continuing for four weeks in a man of his years was probably not due to catarrhal jaundice.

His skin, eyeballs, and mucous membranes were deeply yellow; many telangiectatic spots were seen on the abdomen. There was definite resistance with tenderness in the epigastrium and gall-bladder region. The liver and gall-bladder could not be palpated. There was an incisional hernia in an old appendectomy scar, pressure upon which caused nausea. Examination of other parts showed nothing significant.

Because of his age, the painless onset, and the persistence of the jaundice it was then thought to be a case of obstruction due to pressure on the outside of the duct, with probability favoring a cancer at the head of the pancreas.

The next day he had an attack of severe colicky pain in his epigastrium, so agonizing that it required two hypodermics of morphin (gr.  $\frac{1}{4}$ ) to relieve him. The pain did not radiate to his back.

*x-Ray Report.*—"Distention of large and small bowel with gas; one circular shell-like shadow in gall-bladder region which may be a stone; stomach small, hypertonic, peristaltic waves move freely and easily, exaggerated and strong, walls of stomach freely flexible throughout; duodenal bulb is visualized with the second, third, and fourth portions of the duodenum, is contracted, irregularly filled and fixed; this deformity suggests displacement plus adhesions." *x-Ray impression:* "Probable neoplasm of the head of the pancreas."

*Urine* was very dark, normal specific gravity, trace of albumin, no sugar, no casts, no urobilin.

The *blood* showed a moderate secondary anemia with 14,000 leukocytes (marked anemia and polynucleosis just before death). Coagulation time three and a half minutes. Blood-sugar 131 mg.

Van den Bergh strong immediate.

Dr. J. B. Carnett operated on March 28th for the removal of the probable gall-stone and to provide drainage for the bile through anastomosis in case a growth in the head of the pancreas was causing obstruction by pressure on the common duct. He found stones in the undistended gall-bladder and common duct, and a subacute pancreatitis which was not obstructing the duct.

A cholecystogastrostomy was done and a bit of the diseased pancreas removed. In spite of the drainage the jaundice did not clear. The microscopic examination of the pancreatic tissue showed only subacute inflammation, but no carcinoma. On the twelfth day he died.

This case appears then to have been one of obstruction of the common duct from gall-stone; the primary obstruction was probably due to passage of a stone, too small to cause pain, but which lodged in the ampulla of Vater; the colic occurring four weeks after the onset of the illness was undoubtedly due to the passage of the large stone found in the common duct; the subacute pancreatitis was secondary to the common duct infection and was causing no obstruction.



Case III.—Obstructive jaundice, painless; palpable gall-bladder; carcinoma of head of pancreas.

The patient, seventy-four years old, was brought in unconscious and no history could be obtained. He is emaciated and unconscious. The skin, mucous membranes, and sclerae are deeply jaundiced. The skin is of leaden hue, giving the peculiar appearance of argyria; it is probably due to the cyanosis of failing heart for the lips are cyanosed.

The lungs show many moist râles. The heart-sounds are of poor quality, no murmurs are heard, there are frequent premature contractions.

The abdomen and abdominal veins are distended. The liver is easily palpated and the distended gall-bladder reaches almost to the navel on the right side. The spleen is not felt. Peristalsis is visible and suggests intestinal obstruction. There is a double inguinal hernia.

The blood shows a marked anemia of secondary type; the blood-chemistry and Wassermann are negative.

The urine is a dark brown, contains a heavy trace of albumin, no sugar, frequent hyaline and granular casts. The icterus index on admission was 75, and now with the jaundice deepening is 140. The van den Bergh was immediate direct on two occasions. An x-ray of the gall-bladder could not be taken because of his helpless condition.

A diagnosis of cancer of the head of the pancreas may be made in this case with fair probability of certainty. The determining symptoms are a silent (painless) jaundice gradually deepening, an enlarged gall-bladder and cachexia. Obstruction from gall-stones causes distention of the gall-bladder in no more than 10 to 15 per cent. of the cases. The reason for this is that continued presence of stones has caused a thickening of the bladder-walls, so that it cannot distend.

Distention with jaundice occurs in obstruction of the duct from without and is seen in carcinoma of the papilla of Vater and carcinoma of the head of the pancreas. In the former jaundice occurs earlier; also it is a rarer disorder.

*Courvoisier's law* bears on this. He said, "With obstruction of the choledochus by stone, distention of the gall-bladder is rare; the organ is usually shrunken; with obstruction of other kinds, on the contrary, distention is the rule; shrinking occurs in only one-half of these cases."<sup>1</sup>

*Later Notes.*—The patient died and the autopsy showed general arteriosclerosis; double inguinal hernia; dilatation of the heart with sclerosed valves; congestion and edema of the lungs; hydrothorax; kidneys sclerosed; liver large, with the appearance of portal cirrhosis; section of it revealed dilatation of the intrahepatic ducts, intense bile staining, numerous carcinomatous nodules; the gall-bladder markedly distended, contains no stones; carcinoma of the head of the pancreas inclosing and obstructing the common bile-duct; spleen congested.

Case IV.—Obstructive jaundice; Hodgkin's disease. Autopsy showed enlarged glands surrounding the common duct.

<sup>1</sup> Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege, 1890, Leipzig, Vogel, p. 58.

This case comes from the special surgical ward of Dr. Hubley Owen.

The patient is a white man of thirty-six years. Three years ago he had a marked cervical adenopathy, which was treated with radium. He improved so much that he was able to resume his work and kept fairly well until five months ago. At that time he "acted lazy" and wanted to sleep all the time. He then became restless and was in and out of bed all day. He vomited occasionally after meals, had fever (reached 105° F.), chills, sweats, particularly at night. Two weeks ago his skin began to grow yellow. There has been a foul odor from his throat. He has lost 80 pounds in the past six months. Urine and feces are incontinent. His mind is clear when aroused.

Examination shows him quiet, stuporous, with yellow skin and eyeballs, moderate exophthalmus, pupils dilated, tongue and lips dry, marked bilateral enlargement of the cervical glands, which are matted so closely together that individual glands cannot be palpated.

There is marked dyspnea with many pulmonary râles and dulness at the bases. There is good resonance at the apices, with a decrease of breath-sounds. The heart-sounds are weak and hard to hear because of the pulmonary noise. There is no increase of manubrial dulness. The smooth edge of the liver is felt three fingerbreadths below the right costal border. The spleen is felt three fingerbreadths below the left costal border. The abdomen is distended and tympanitic, with movable dulness in the flanks. There is no abdominal pain or tenderness. The axillary glands are not palpable; the inguinal moderately so. An x-ray taken of his chest shows no increase of sternal dulness.

The blood showed a marked anemia with 25 per cent. lymphocytes, later the lymphocytes were reduced to 20 per cent.; no eosinophils were found: poikilocytes and achromic red cells. The Wassermann was negative; icterus index 15; van den Bergh biphasic.

The urine was brown, contained a light cloud of albumin and an occasional hyaline cast.

His temperature, pulse, and respiration have been constantly above the normal.

A diagnosis of Hodgkin's disease is made in this case because of the enlargement of the cervical glands, the decrease in the lymphocytes, the marked improvement after the use of radium, the preliminary period of lassitude, weakness, and sleepiness, and the marked constitutional disturbance. Tuberculous adenitis must be considered, but in this there will be found an increase of lymphocytes, a tendency of the glands to suppurate and, with such marked systemic disturbance, marked involvement of the lungs. Jaundice is an uncommon complication of Hodgkin's, but can be accounted for by the pressure of enlarged glands on the common duct. I have seen 1 case of jaundice due to pressure from syphilitic glands.

*Later Notes.*—The patient died and the autopsy showed fluid in the pleural and peritoneal cavities; healed tuberculosis of the lung apices; Hodgkin's nodules in the lungs, spleen, kidneys, liver; enlargement of lymph-nodes surrounding the common duct and almost occluding it.

Case V.—Obstructive jaundice; adenocarcinoma of papilla of Vater; secondary biliary cirrhosis; xanthomatosis; hypercholesterolemia.

This case was reported in full by Drs. Boston and Jodzis and will be published in the Jour. Amer. Med. Assoc. under the title of "Cholesterolemia and Adenocarcinoma of the Papilla of Vater."

This man of forty-four years is an example of obstructive jaundice, who shows most interesting and unusual symptoms. His illness began a year and a half ago, when the first symptom, pruritus, appeared. He noticed jaundice in his eyeballs one month later; this "spread all over his body in two or three weeks." I am inclined to think that earlier it was so light his inexperienced eyes did not detect it. Itching has been so severe, particularly at night, that his sleep has been much disturbed.

His stools were putty colored and constipated for eight months. Then he began to have four to six a day and the color alternated between gray and yellow. There has never been any pain in the abdomen.

About five months after the onset small xanthomata appeared on both elbows. These have continued to appear until they are now seen in great numbers between the fingers, on the palms, elbows, knees, lower lip, and left lower chest. These last appeared on the site of the vesicles of herpes zoster about one year ago. At the time of the appearance of herpes the jaundice and pruritus lessened. This date coincides with that of the irregular return of color in his stools. There has been no hemorrhage from the stomach or bowels. In spite of a good appetite he has continued to lose weight until lately, when he gained 7 pounds.

The previous history includes childhood diseases, an accident which badly cut his scalp, arms, and legs, two years ago. He denies venereal disease and alcohol, but he is reported to have been a heavy drinker; uses tobacco moderately. The family history is unreliable.

*Examination.*—He is a thin man showing a great loss of weight; his body, including the scleræ, is deeply jaundiced, the exposed parts of the body being bronzed. There are depressed scars on his scalp, legs, and arms which look luetic. The xanthomata are seen as yellowish nodules on various parts of the body. The arms and legs have a peculiarly dark freckling and the hair on them is broken from continual scratching.

The left pupil is smaller, but both pupils react to light and accommodation. There is but one tooth left and that is badly decayed; the tonsils are enlarged and exude cheesy material when pressed upon. The whole chain of cervical glands, anterior and posterior, are moderately enlarged. The lungs and heart are practically negative. The liver extends below the navel, is smooth, hard, and insensitive. There is a suspicion of a palpable gall-bladder; the spleen is just palpable. There is no edema or cyanosis of the extremities.

The blood shows a marked secondary anemia; Wassermann 4+; cholesterol 960 to 1020 mg. (normal 170–200 mg.); sugar 65 mg.; icterus index 45; van den Bergh immediate.

Urine: Dark amber, specific gravity 1.017, trace of albumin, no sugar, occasional hyaline casts, bile-pigment.

x-Ray of gall-bladder failed to visualize it.

A diagnosis of secondary biliary cirrhosis is made because of the marked jaundice of the obstructive type; the greatly enlarged liver without ascites, and the enlarged spleen.

It is hard to determine the cause of the obstruction; we may suppose that with such high cholesterolemia the bile-ducts are clogged, preventing the outflow of bile. The source of the excessive cholesterol is unknown.

*Later Notes.*—The patient died and the autopsy showed the tissues well stained with bile, the liver twice the normal size with firm nodules which are green on section with the lobular markings lost. The surface seems composed of greenish areas separated from each other by fibrous tissue. It is grossly like biliary cirrhosis. The gall-bladder is small and partly collapsed; all the bile-ducts are markedly enlarged and lined with a bright yellow encrusting material. The common duct is the size of the index-finger; there is a definite narrowing at the papilla of Vater, which is firm and fibrous. The pancreas is of normal size and does not press on the common duct.

Microscopically, the liver tissue showed biliary cirrhosis and the papilla, adenocarcinoma. This shows that while the ducts were encrusted with the cholesterol, they were not obstructed by it. The obstruction was the carcinoma at the papilla.

Case VI.—Catarrhal jaundice (infective) in a man of fifty years.

This man comes to us from the House of Correction where he was committed for alcoholism.

For a month he has had a cough with moderate fever and chills. A week ago his companions noticed his skin was yellow. Four days later it became pronounced enough for him to notice it himself. There is no history of digestive disturbance before the jaundice appeared. He has a dull pain in the left shoulder and nape of the neck; he has frequent frontal headaches; appetite is fair; no digestive complaints; bowel movements of dull gray, glistening appearance, occur daily. There is no history of intravenous injections of arsenic.

The previous history shows typhoid fever and pneumonia when he was thirty-five, irritability and tremors after drinking, delirium tremens once, has just finished a spree lasting six months, in which he claims he took a quart of cheap whisky a day; gonorrhea; denies syphilis.

Examination shows him to be a well-nourished and well-preserved man for his years and dissipations; he does not seem seriously ill; the skin, mucous membranes, and sclerae are definitely jaundiced; the mouth is foul from decayed teeth and lack of care. The lungs and heart appear to be normal. The abdomen is not distended; the liver is felt two fingerbreadths below the right costal margin, but is not tender. The gall-bladder and spleen cannot be felt.

The blood, including the chemistry, is practically normal; the Wassermann is 4+, with cholesterin antigen; the icterus index is 140; van den Bergh biphasic; a second test gave a delayed reaction.

The urine is of increased specific gravity, mahogany color, contains a trace of albumin, and an occasional hyaline cast, but shows no urobilin.

The x-ray failed to visualize the gall-bladder. The pulse, temperature, and respiration have been normal throughout the illness.

A bile drainage was done and while a fair amount of bile was extracted, there was no improvement in the jaundice. Now, after three weeks, he is improving. The jaundice is lessening, the stools show an increasing amount of brown, and the urine is lighter.

Despite his age of fifty, a diagnosis of catarrhal jaundice is made because it occurred after a debauch and a respiratory infection, and is showing a tendency to disappear. He showed little constitutional disorder. While the first van den Bergh was biphasic and indicative of an obstructive factor, the second was delayed (non-obstructive). Some observers classify catarrhal jaundice as obstructive, and while the origin of the condition is infective, undoubtedly obstruction takes place. The disorder usually occurs in young people. Painless jaundice in one of fifty, even though he show no emaciation, makes us think of cancer of the head of the pancreas. His improvement probably disproves this. The positive Wassermann turns our attention to spirochetal infection of his liver and to syphilitic enlargement of the lymph-nodes about the common duct. But improvement without antisymphilitic treatment makes this unlikely.

*Later Notes.*—After four weeks the patient was practically well. The urine and feces were of normal color and the jaundice nearly gone.

**Case VII.**—Toxic jaundice, occurring after intravenous injection of arsphenamin; syphilis.

This negro boy of sixteen was admitted from the House of Detention because of jaundice, which appeared one week after the third injection of arsphenamin. He has been considerably prostrated, with an elevation of temperature, pulse, and respiration for two weeks. He states he had a chancre several months ago.

He is moderately jaundiced, the discoloration showing quite clearly in the palms and scleræ. He has narrow lower incisor teeth and peg-shaped upper teeth, with a trifle of notching. This makes us think he has congenital syphilis. He is a moron; this, coupled with the appearance of the teeth, throws a doubt on his statement concerning chancre.

The liver and spleen are enlarged. Examination of other organs reveals nothing significant. The blood shows a moderate leukocytosis; icterus index 60; van den Bergh biphasic; Wassermann 4+; chemistry normal.

The urine shows a heavy trace of albumin, many pus-cells, no casts, no bile-pigment.

This case has some of the characteristics of catarrhal jaundice, but as it appeared soon after the injection, it seems as if the arsenic was the cause. Granting that he had a chancre recently this might be considered as the jaundice which occurs, rarely, in the early stage of syphilis. But this clears up with specific treatment. His youth and the enlargement of the liver and spleen makes us think of biliary cirrhosis; but against that diagnosis is the fact that his jaundice is now beginning to fade.

Jaundice following arsphenamin injections takes on the characteristics of acute yellow atrophy at times and is then followed by death.

**Case VIII.**—Hemolytic jaundice; pernicious anemia.

This negro woman of thirty-five comes into the hospital complaining of great weakness, stiffness, and numbness of the extremities.

She has been sick for five years with weakness growing progressively worse, anemia, gastric disturbances, dyspnea, edema of ankles which disappeared with water restriction, nosebleed two or three times a week for two years, continuous headache. She has lost 70 pounds in three years.

*Examination.*—The great loss of weight is noted in her appearance, but she cannot be considered emaciated. There are dark brown pigmented spots noted over the body. The scleræ are pearly white, the mucous membranes very pale with a yellowish tint. The skin is dry, the joints stiff. She has no teeth; the tongue is smooth and pale. The heart is slightly enlarged, a systolic murmur is heard at the apex and transmitted to the axilla, the pulmonic second is accentuated. The pulse is rapid and regular, the vessels sclerosed. The lungs are clear. The liver is just palpable, the spleen is not. The ankles are a bit swollen and pit on pressure.

At this time the blood shows hemoglobin 30 per cent., red blood-cells 1,150,000, white blood-cells 6000; color index 1.3; poikilocytes, anisocytes, nucleated red cells, megalocytes. Various counts made show little variation from this. Icterus index 17; van den Bergh at first was negative and later was delayed (non-obstructive jaundice). Wassermann was negative.

The gastric analysis showed an absence of free hydrochloric acid, a decreased total acidity, and an absence of lactic acid.

With this blood report and history the diagnosis of pernicious anemia is justified. The jaundice is scarcely perceptible and corresponds to her icterus index of 17.

**Case IX.**—Hemolytic jaundice; Banti's disease.

This white woman of twenty-eight has recently been admitted to the hospital because of hemorrhage from her stomach. She has had a number of such attacks: the first when she was ten, and after violent exertion; the second when she was twenty, and seven months after the birth of her first child this was very severe; the third when she was twenty-four, and six weeks after the birth of her second child; the fourth last week, six months after the birth of her third child, this hemorrhage was very large. She complains of a mass in her left abdomen which is sore enough to keep her from lifting things. This soreness has increased before each hemorrhage and she thinks she becomes slightly yellow then, but neither symptom has been marked enough to predict the hemorrhage. She has had a little dyspnea and palpitation of the heart on exertion; there has been no edema or cyanosis.

She has marked indigestion with certain foods; hemorrhoids have appeared from time to time, but they have never bled freely. She has had no other complaints.

*Examination.*—Blood-pressure 105/55. Temperature, pulse, and respirations are increased. She lies quietly in bed and with the light in the right position shows a slight yellow tint of the skin and scleræ. The teeth are broken and decayed, the tongue red and dry, the throat injected, the left tonsil large and exuding pus on pressure. The lungs are clear. There is a soft systolic murmur over the heart which is not transmitted. The abdomen

is relaxed and contains no fluid. The liver cannot be felt. The spleen is hard, sharply defined, and reaches nearly to the navel. There are three ecchymotic spots on the legs.

Her *previous history* includes several attacks of malaria when a child which responded easily to quinin; severe influenza in 1918; continued fever with each hemorrhage.

Blood: Hemoglobin 35 per cent., red blood-cells 1,960,000, white blood-cells 5100; marked acromia, poikilocytosis, and anisocytosis. This marked anemia is partly due to the recent severe hemorrhage. Negative for malaria, typhoid, and paratyphoid. Wassermann negative; fragility of red corpuscles increased. Urea nitrogen and uric acid increased; sugar normal. Icterus index 20, van den Bergh delayed.

The urine is negative, contains no urobilin.

A diagnosis of Banti's disease is made because of the large spleen, profuse hemorrhages, the marked anemia, and the non-obstructive jaundice.

Gaucher's disease may be ruled out because of the absence of the wedge-shaped thickening of the conjunctivæ, of pigmented areas of the skin, and of similar disorder in the family.

These 2 cases show the mild degree of discoloration which occurs in hemolytic jaundice. It is the least prominent symptom.

If this be Banti's disease it is in the first stage. The enlarged spleen should be removed after her blood has improved.

The risk from splenectomy is small and the results following it are very satisfactory—the disease is stayed in its progress at least, and some cases are apparently cured. If the removal be delayed until the liver enlarges and ascites occur, the operative risk is much greater and the results very poor.

## CLINIC OF DR. T. GRIER MILLER

Assisted by LOUIS M. LIEBERMAN, Medical Student, '30.

FROM THE GASTRO-INTESTINAL CLINIC OF THE UNIVERSITY OF  
PENNSYLVANIA HOSPITAL

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### ACTIVE CONGESTION OF THE STOMACH AS AN EXPLANATION OF THE MECHANISM INVOLVED IN THE GASTRIC HEMORRHAGE OF SPLENIC ANEMIA. PRESENTATION OF FOUR CASES WITH HEMORRHAGE BEFORE AND AFTER SPLENECTOMY.

MASSIVE gastric hemorrhage occurs most frequently in cases of gastric and duodenal ulcer, of carcinoma of the stomach, and of certain diseases of the liver and spleen. In the instances of ulcer and carcinoma the gastric blood-vessels, often arterial, are opened by an eroding process from without, while in the hepatic diseases the blood escapes from the gastric or esophageal veins as a result of rupture incident to stretching and thinning of the vessel walls and to increased pressure from within, these conditions being dependent upon obstruction to the portal blood flow. The explanation for the gastric hemorrhage of the splenic cases, chiefly those of splenic anemia, is not so obvious and most authors seem content to agree with Osler,<sup>1</sup> who states that it is due to "the intimate relations which exist between the vasa brevia and the splenic circulation." It is with this problem that we wish to deal today, but before discussing it further I shall ask Mr. Lieberman to present an outline which he has prepared of the records of the case of splenic anemia that I now have before you. He will later give you a briefer outline of three other similar cases in our series and refer to some of the data on the entire group of 14 cases that has been on our service during the past eight years.



MR. LIEBERMAN: Case I.—This patient, J. G., a boy, now eighteen years of age, was first admitted to this hospital on August 30, 1926. One year previously, after a game of football, he had noticed that his stools were bloody. On the following day he had vomited coffee-ground material and fresh blood. Nine months later, and three months previous to his first admission, after strenuous running, he had vomited blood and his stools were bloody. On the day previous to admission he had been running a great deal and the next morning had vomited about a quart of blood, this being the third such occurrence within the year. Again that afternoon he had suffered from hematemesis. He had had no symptoms previous to his hemorrhages except that several years before he had complained of severe pain over the left lower chest, being almost unable to move, had become very pale, and his father had thought he was going to die. During the year of his known hemorrhages he had been somewhat dyspneic on exertion, had lost 5 pounds in weight, and thought that he had been more or less pale. Measles, whooping-cough, and pneumonia had been the only diseases of his childhood. His family history was negative except that his mother had had three miscarriages, and that three of seven brothers and sisters had died: one of whooping-cough, another of dysentery, and the third of "spasms." His social history was negative.

Upon physical examination at that time, it was noted that the boy was rather underdeveloped for his age (sixteen years) and that no axillary or pubic hair was present. Pallor was fairly marked, especially about the mucous membranes. His heart was not enlarged, rhythm was normal, and no murmurs were heard. His abdomen showed a little bulging in the left, upper quadrant and the spleen could be felt below the costal region.

On the evening of his admission, within six hours of his last attack of hematemesis, his leukocytes numbered 22,900 and the hemoglobin was down to 54 per cent. He vomited more blood during the night, and a complete blood-count on the following morning showed: Red blood-cells, 2,970,000; white blood-cells, 17,400, of which 84 per cent. were neutrophils; and hemoglobin, 44 per cent. There was some variation in the size and shape of the red blood-cells. He vomited again during that night and had blood in his stools the next morning. The subsequent blood studies are given in Table 1, which also indicates the dates of his six blood transfusions, the amounts of blood administered and other laboratory findings.

His spleen steadily increased in size, soon reaching a level 8 cm. below the costal margin in the left nipple line. A notch along its mesial border was easily felt. The gastric bleeding continued irregularly, although some stool examinations were negative even to the occult blood test, and the degree of anemia increased in spite of repeated transfusions. On September 23d he vomited about 1 pint of blood, but there was no evidence of bleeding after that.

Because of the repeated gastric hemorrhages associated with splenomegaly and anemia and the absence of other cause for such hemorrhage a diagnosis of splenic anemia was made and splenectomy was advised. This was performed by Dr. Eldridge L. Eliason on October 4th.

The spleen proved to weigh 628 gm. and to measure 17 x 11 x 6 cm. The surface was somewhat roughened and showed a number of irregularly

TABLE 1  
BLOOD FINDINGS IN CASE I

Date.	Hb.	R. B. C.	W. B. C.					Blood-platelets.	Remarks.
			Number.	Differential.					
				P.	L.	M.	E. & B.		
8/30/26	54		22,000						Six hours after hematemesis.
8/31/26	44	2.9	17,400	81	13	3	0		Further bleeding that night.
9/1/26	30		27,200						Transfusion, 250 c.c.
9/2/26	30		23,200					76,800	Wassermann negative. Touriquet test negative. Bleeding time, 2.5 min.; retraction of clot, normal. Fragility, 5 to 0.325.
9/7/26	32	1.6	6,500	82	11	3	3		Van den Bergh test negative; nucleated red cells, basophilic degeneration, and polychromatophilia. Fragility of R. B. C., 0.475-0.3.
9/11/26	24	1.6	4,700	58	39	2	0		After second transfusion.
9/13/26	16	1.4	5,000					160,000	
9/15/26									Third transfusion, 500 c.c.
9/16/26	28	1.7	4,000	69	26	4	1		
9/23/26	30	1.2	2,300	74	23	3	0		After fourth transfusion of 500 c.c. and vomiting of more blood. Bleeding and coagulation times normal.
9/29/26									Fifth transfusion, 500 c.c.
10/1/26	42	2.5	2,500	63	28	7	3		Retenulated cells, 4 per cent.
10/4/26									Splenectomy.
10/18/26	46	3.2	5,500	72	0	0	0		Discharged, 10/19/26.
6/13/28	43	2.4	11,200	71	26	2	1	280,000	Second admission after melena. Wassermann negative. Bleeding and clotting times normal.
6/22/28	42								Esophagoscopy.
8/4/28	31	2.7	8,000	73	24	3	0	470,000	Third admission, after hematemesis and transfusion of 500 c.c.
8/5/28	28	3.0	9,000	69	22	9	0	440,000	

outlined blanched areas. The cut surface proved to be brownish-red in color and did not bulge. The blanched areas on the surface did not extend into the tissue under the capsule. The blood-vessels were numerous and large. The malpighian bodies were well recognized throughout. The microscopic diagnosis was chronic splenitis.

He ran a slight irregular fever for a week after the operation, but made a good recovery, his blood-picture showing improvement, and he was discharged from the hospital on October 19th, fifteen days after the operation.

The surgical follow-up records indicate that he reported back on July 12, 1927, stating that he had gained 18 pounds in weight and had had no symptoms of any kind. He looked the picture of health. Again on November 1, 1927 he reported that his condition was entirely satisfactory.

The boy next appeared at the hospital on June 14, 1928, being admitted to one of the medical wards. It was then determined that he had remained in good health from the time of his discharge, almost two years previously, until June 4th, ten days before this admission, and had gained 42 pounds in weight during that time. Upon the above date (June 4th) he had developed a sore throat and had vomited. No blood was noticed in the vomitus, but subsequently his stools were tarry black. The melena persisted and he became more and more pale. No further vomiting occurred. Physical examination on that admission revealed a more normally developed young boy, but still somewhat below the average. His tonsils were moderately inflamed and some of the anterior cervical lymph-glands were enlarged. A faint systolic murmur was noted at the cardiac apex, but otherwise the heart was entirely negative. The liver could not be felt. The important laboratory data obtained are given in the table.

In an attempt to determine the source of his hemorrhage after splenectomy an esophagoscopy was done by Dr. Gabriel Tucker on June 22d, and it was found that throughout the lower third of the esophagus there was marked dilatation of the veins, with the formation of pedicle masses, the appearance being typical of well-developed varices in the lower end of the esophagus. The abdominal esophagus also showed marked varices. No point of hemorrhage was seen. There being no further evidence of bleeding, the patient was discharged from the hospital June 29, 1928.

For the third time he has now come into the wards, having been admitted on August 4th, and again because of hematemesis. This occurred during the afternoon of the day of admission. He first noticed a headache with some ringing in his ears and had a pain in his epigastrium. He was put to bed and at about 3 o'clock in the afternoon vomited what his mother took to be a full quart of blood. Upon arrival here he presented the picture of marked hemorrhage and was immediately given a transfusion of 500 c.c. of blood. He now appears in fairly good condition, showing no signs of shock, but is still quite pallid and complains of weakness. In spite of the transfusion his blood presents evidence of a marked secondary anemia. (See Table 1.)

COMMENT BY DR. MILLER: The original diagnosis of this case offered little difficulty and depended, as Mr. Lieberman

has said, on the presence of a greatly enlarged spleen, repeated gastric bleeding, and the absence of any other cause for the hemorrhages. It is probable that the spleen had been enlarged for a long time before its recognition on his first admission two years ago, and undoubtedly he had a gastric hemorrhage at the time (several years before that admission) when he became very pale and it was thought that he was going to die. Such a prolonged course of the disease is common, as is also its occurrence in children and young adults. Anemia is commonly present and is of the secondary type, except that a leukopenia without polymorphonuclear increase is usually associated. The presence of both a leukocytosis and a neutrophil increase in this patient when first seen are accounted for by his recent hemorrhage; some of the later counts, however, showed the usual leukopenia. The resistance of the red blood-cells is usually unchanged, though the figures in this case indicate a slight loss of resistance. This may have resulted from the transfusion of blood a week before, and the presence of nucleated red cells and of the unusual number of reticulated cells in our patient may have been due to the repeated hemorrhages. The reduced platelet counts before splenectomy are not unusual but by no means constant, and this may have been a factor in his tendency to bleed.

Other points in the diagnosis and in the differential diagnosis need not be referred to at this time as we are primarily interested in the gastric hemorrhages that are so characteristic, and which incidentally occur only rarely in other diseases of the spleen. It has been stated frequently that splenectomy stops bleeding from the stomach, but especial attention is called to the fact that this boy has continued to have profuse hemorrhages since his operation. To emphasize this point I will ask Mr. Lieberman to give us a very brief statement regarding the three other of our 4 cases of splenic anemia that have had postoperative bleeding.

MR. LIEBERMAN: Case II.—I. L., male, was first admitted on June 26, 1920, at the age of nineteen. His family history was negative and he had had no symptoms except frequent and profuse epistaxis as a child, until October 6, 1918, when he began to have epigastric pains after meals. Seven days later,

after lifting a heavy weight, he developed a sharp pain in his midepigastrium, and six hours later vomited a large quantity of blood. Again on May 4, 1920, about six weeks before his admission, he lifted a weight, felt sick, and vomited a large quantity of blood.

Upon admission he was quite anemic and his spleen extended 4 cm. below the umbilical level. Gastric analysis showed some hyperacidity. Wassermann was negative. Roentgen-ray study of the gastro-intestinal tract was negative, except for the shadow of an enlarged spleen. Reticulated cells were within normal limits. The fragility of the red cells was slightly increased. There was a persistent leukopenia. Urobilin content of the feces was reduced below normal. A diagnosis of splenic anemia was made and a splenectomy was done on July 15th. Transfusions were done before and after the operation.

The removed spleen weighed 750 gm. It cut with evident resistance and a grating sensation. Sections showed an increase of young connective-tissue cells. Fibrous tissue septa were increased in thickness and showed hyaline changes. The blood-vessels were imperfect, showing fairly good internal lining, but little media or adventitia. Some of the larger blood-vessels showed fibrinous clots.

He was readmitted on May 1, 1921, because of weakness and dizziness, following light work in the garden. Following this he had noted that his stools were very black. Again his anemia was very marked, but his leukocytes numbered 12,000. Reticulated cells at this time were increased to 5 per cent. and some nucleated red cells were observed. Fragility of the red cells at this time also was normal. A second gastro-intestinal roentgenologic study was negative for peptic ulcer.

Third admission was on October 9, 1921, the day after a gastric hemorrhage. This again had followed exertion of loading 50-pound hampers of beans onto a car. He stated that he had vomited about a quart of blood, and on the way to the hospital he fainted, being unconscious for five minutes, and after that vomited more blood. Leukocytes were increased to 13,300. Fragility test was negative.

Fourth admission was on November 28, 1921 because of the passing of black, tarry stools, this occurring after working for a few hours in a store. His blood at this time showed only a very slight degree of anemia. Leukocytes numbered 10,100. Third gastro-intestinal study by the Roentgen ray was negative but for a defect in the lesser curvature of the stomach near the cardiac end, presumably due to adhesions.

On May 1, 1923 he was admitted for the fifth time, having been in reasonably good condition until two days before, when, after playing baseball, he became excessively thirsty, drank water, was nauseated, and vomited a quart or two of bloody material. Hemoglobin was down to 36 per cent. Leukocytes numbered 20,900, and the red cells were reduced to 2,000,000.

Six months later, on October 29, 1923, he again came to the hospital because of hematemesis, this having occurred on the day before admission. There was no history of strain preceding this attack. Hemoglobin was 46 per cent., red cells 2,560,000, and blood-platelets numbered 185,000. An exploratory laparotomy was advised, but this the patient refused.

His seventh admission occurred on January 21, 1926. While riding on a train he had become nauseated and had tasted blood, but did not vomit. Later he had bloody stools. On the day following his admission he vomited 1300 c.c. of bloody material, and transfusions were necessary. Immediately after the hemorrhage his platelets numbered 209,000.

After the next hemorrhage he was admitted to another hospital in the city and there again was advised by Dr. John B. Deaver to have a laparotomy, but he again refused.

On June 6, 1927 he returned to this hospital for the eighth time, and then because of bloody stools. His blood showed no special degree of anemia and after a short rest he was discharged.

His final admission, and this time for the purpose of having a submucous resection of his nasal septum performed, was on February 23, 1928, when he stated that he had had one attack of hematemesis since his last discharge and had passed tarry stools for a month, but there had been no evidence of bleeding just preceding this admission. His blood-count was practically normal. His platelets numbered 251,000. Van den Bergh test was negative. Coagulation time, bleeding time, fragility of the red cells, and clot reaction were all normal. Wassermann was again negative.

An esophagoscopy was performed by Dr. Gabriel Tucker, this showing esophageal varices involving the lower third of the esophagus and the cardiac end of the stomach. Tortuous nodules covered with normal mucosa were found at irregular points. Some of them were distinctly blue in color.

COMMENT BY DR. MILLER: This patient's story is very striking and emphasizes, as no mere statement can, the tremendous handicap that some of these patients suffer, even after a splenectomy, because of their tendency to gastric hemorrhage. It will be noted that in almost every instance the hemorrhage in this case followed some physical strain: lifting weights, working in the garden, throwing hampers of beans into a car, and playing baseball. Similarly, the boy before you had his first hemorrhage (before operation) after running, and later after an upper respiratory infection, this doubtless being associated with some increased strain on his circulation. We may still further emphasize this tendency to a continuance of gastric hemorrhages after splenectomy by the two remaining cases to be very briefly referred to.

MR. LIEBERMAN: Case III.—S. W. W., aged twenty-one years, was admitted to the private service of Dr. Alfred Stengel on October 29, 1923, because of hemorrhages from the bowel. He had had a splenectomy for splenic anemia performed five years previously, at the age of sixteen, by Dr. Charles H. Frazier, having had gastric hemorrhages beforehand. Afterward he had

had two hemorrhages, the first on April 22, 1928, and the second four weeks before his admission. It was stated that his red cells had been reduced to 1,000,000 after the second hemorrhage. At the time of his admission his red cells numbered 3,500,000 and the hemoglobin amounted to 55 per cent. Van den Bergh test was negative. The stools showed only occult blood. Coagulation and bleeding times were normal. Urobilin content of the stools was normal. Gastro-intestinal Roentgen-ray study showed adhesions above the pylorus and some deformity about the duodenal cap.

He was readmitted on February 26, 1928, and then stated that he had had ten attacks of hematemesis during the past five years. In July, 1926 he had been operated on in Cleveland for duodenal ulcer, but none was found. The last hemorrhage had occurred just one month before his admission. An esophagoscopy by Dr. Gabriel Tucker showed marked varicosities in the lower thoracic and abdominal esophagus. Dr. Stengel advised an exploratory laparotomy and this was subsequently performed by Dr. Eldridge L. Eliason on May 2, 1928, when there were found many large varicose veins, especially over the anterior surface of the stomach at the cardiac end. The adhesions were so extensive that it was impossible to expose the stomach sufficiently to do a gastrotomy.

Case IV.—B. S., a girl of twelve years, was referred to the hospital by Dr. R. A. Kern for the first time on October 6, 1924, complaining of weakness, and she stated that she had vomited a quantity of blood eight months previously. At that time she had been admitted to another hospital and a transfusion given. Splenectomy was refused by her parents. Stools had subsequently been black from time to time and three other transfusions had been given.

Physical examination revealed a definite pallor and an enlarged spleen extending down to the level of the umbilicus. Blood studies showed a marked anemia with a low leukocyte count. Other examinations were essentially negative.

A diagnosis of splenic anemia was made and splenectomy advised. The operation was performed by Dr. Eliason, and she was discharged in good condition.

She was readmitted on December 11, 1925, because of recurrence of her gastric bleeding. Gastro-intestinal roentgenologic study was negative except for evidence of some constriction of the duodenal cap, probably due to adhesions. She had a secondary anemia and a leukocyte count of 24,800.

She was again admitted to the Wards on October 10, 1926, because of gastric hemorrhages which began during a menstrual period and kept up for a week. Her blood showed only 750,000 red cells with a hemoglobin of 12 per cent. and 25,800 leukocytes. After several transfusions the blood-picture improved, the hemoglobin finally getting up to 73 per cent. and red cells to 4,140,000. At this time she submitted to an exploratory laparotomy. Extensive adhesions were found along the inner aspect of the scar of the previous operation and the slightest traction of the gastrohepatic omentum caused hemorrhage. The stomach could not be drawn into the wound on account of the extensive adhesions, but a cholecystoscope was inserted for the purpose

TABLE 2  
GENERAL DATA ON FOURTEEN CASES OF SPLENIC ANEMIA

No.	Year first admitted	Sex.	Age at 1st adm.	Duration of symps. before 1st admission.	Hemorrhages			Fever.	Wass.	Splenectomy.	Remarks.
					No.	Emesis.	Melena.				
1	28	M.	8	1 yr.	3	+	+	+	-	+	Convalescing from operation in hospital.
2	21	F.	12	8 mos.	2	+	+	+	-	+	Recurrence of hemorrhages after operation. Second operation showed varicosities and adhesions. (Case IV in text.)
3	26	M.	15	1 yr.	4	+	+	+	-	+	Now in hospital with second recurrence of hemorrhage after operation. (Case I in text.)
4	20	M.	19	18 mos.	2	+	+	+	-	+	Nine readmissions for hemorrhage after operation. (Case II in text.)
5	21	F.	20	2 yrs.	4	+	+	+	-	0	Refused operation. Unable to locate.
6	23	M.	24	9 yrs.	10	+	+	+	0	+	Recurrences after operation. Reoperated 1928. Varicosities of stomach found. (Case III in text.)
7	28	M.	21	12 yrs.	++	+	+	+	-	0	Refused operation. Has had recurrence of gastric hemorrhages.
8	27	F.	27	5 yrs.	0	0	0	+	-	+	Liver has greatly enlarged; anemia persists. Has had abortion with marked vaginal hemorrhages.
9	27	M.	34	16 mos.	++	+	+	0	-	0	Died of gastric hemorrhage just before splenectomy was to be done. Hepatic cirrhosis.
10	21	M.	38	5 yrs.	++	+	+	0	-	+	Discharged improved. No follow-up.
11	23	M.	40		9	+	+	+	+	+	Died after operation.
12	21	M.	45	18 mos.	3	+	+	+	-	+	Refused operation here, but done elsewhere in 1927. Able to work since.
13	27	F.	19	20 yrs.	++	+	+	+	-	+	Died following operation.
14	24	F.	62	2 yrs.	++	0	+	+	-	+	Fair condition, but anemia persists.



of viewing the greater and lesser curvatures. Many dilated veins were found but none appeared to be thrombosed.

COMMENT BY DR. MILLER: Before discussing further this matter of gastric bleeding before and after splenectomy in cases of splenic anemia I wish to refer to some of the more general data which Mr. Lieberman has compiled from the records of the 14 cases studied on this service during the past eight years. His table (Table 2) shows: (1) That males predominated (9 to 5); (2) that the ages ranged from eight to sixty-two years; (3) that the known duration of symptoms was from one to twenty-nine years; (4) that 11 of the 14 cases had suffered from hematemesis (one patient having had ten attacks), and that 2 others had noted gross blood in the stools (this leaving but one without evidence of gastric bleeding); (5) that 10 had some fever during observation in the hospital and before operation; (6) that the Wassermann reaction was negative in all but one case; (7) that 12 had a splenectomy, the other 2 refusing operation; (8) that 4 had a recurrence of gastric hemorrhage after operation, and (9) that of the other 8 splenectomized, 2 died following operation, 1 is still in the hospital, and the other 5 were discharged in satisfactory condition (2 of these are still anemic and 3 cannot be located).

All of these cases had markedly enlarged spleens and an anemia which varied from time to time, the variation depending, in part at least, upon the occurrences of hemorrhages and transfusions. Independently of the hemorrhages none of the cases showed evidence of increased blood formation or a markedly abnormal platelet count. The fragility of the red cells was normal or slightly increased. All the other special blood studies gave results within normal limits.

It is well known that a portal cirrhosis of the liver eventually develops in some cases of splenic anemia (then known as Banti's disease), but none of our cases had progressed to such a stage as to present clinical evidence of this complication.

Now that we have, as a result of this brief consideration of our clinical material, a general idea of the disease "splenic anemia," we will return to a discussion of its most dramatic

symptom or complication—gastric hemorrhage. This occurred before splenectomy in 13 of our 14 cases (93 per cent.) and in 11 of them the blood was vomited. It occurred after splenectomy in 4 of the 12 cases that underwent operation (33 per cent.). W. J. Mayo<sup>2</sup> in 1919 stated that he had had but one case of such postsplenectomy hemorrhage and that such experiences were unusual, but later, in 1926, after following up a series of 114 of their splenectomized cases, he<sup>3</sup> found that 10 per cent. of those leaving the Mayo Clinic had died of hemorrhage, usually from the stomach. Hanrahan<sup>4</sup> had five such postoperative hemorrhages in 14 cases that had been bleeding before operation. This frequency is too great to be accounted for by unrelated conditions and suggests at least that the cause for the preoperative bleeding from the stomach is not relieved by the operation of splenectomy.

What then is the cause of the gastric bleeding in the first place? I wish to ask Mr. Lieberman to answer this question by giving us a statement of the causes that he has found suggested in the literature which he has covered on this subject.

MR. LIEBERMAN: There is much confusion in the literature regarding this question and no one gives an explanation that is entirely satisfactory. The most common causes assigned are as follows:

1. An altered condition of the blood, manifested by a low platelet count, this leading to an escape of blood through the vessel walls.

2. Mechanical interference with the circulation of the stomach as a result of the drag of the enlarged and heavy splenic organ.

3. Stasis in all the veins of the stomach resulting from portal obstruction incident to periportal cirrhosis of the liver or to thrombosis of the portal vein.

4. Interference with the return circulation from the stomach through the splenic vein alone, due to splenic vein thrombosis.

5. Overdistention of the gastric veins resulting from an increased blood-supply to the stomach along with that to the spleen.

COMMENT BY DR. MILLER: These five causes, roughly speaking, may be grouped into two: An altered condition of the blood and an altered condition of the gastric blood-vessels. Rosenthal<sup>5</sup> particularly is responsible for the suggestion that the primary trouble, in some of the cases at least, is dependent upon a change in the constituents of the blood, a reduction in the blood-platelets, a thrombocytopenia. This platelet reduction undoubtedly occurs, as he has demonstrated, and it probably accounts for the bleedings that sometimes develop in other parts of the body, as, for instance, the epistaxis that our Case II had in earlier life; others have had definite purpuric manifestations. But it is difficult to explain the sudden large gastric hemorrhages on such a basis alone. Rosenthal himself admits that some cases have very high platelet counts, some even over a million, and for these he invokes another explanation—thromboses of the vessels draining the stomach. It seems more probable that some single condition explains all of the cases.

All of the other assigned causes imply a dilatation and rupture of gastric veins. The existence of such varices would seem well proved since they have been found repeatedly at autopsy and operation. Furthermore, in 3 of our reported cases, Dr. Tucker demonstrated by direct inspection marked enlargements of the lower esophageal and gastric veins. The question resolves itself then into an explanation for the gastric and esophageal varices. Once these are admitted one can readily understand how physical strain, an infection whipping up the circulation or the trauma of gross food particles, may cause rupture and hemorrhage.

Let us then examine further into the causes assigned for the varices. In the first place, we may dispose of the suggestion that the drag of the heavy spleen is important by considering that the equally heavy or heavier spleens of certain other diseases do not produce such hemorrhages. Chaney<sup>6</sup> found the spleens removed from cases of Gaucher's disease at the Mayo Clinic to weigh on the average 3031 gm., and those from the lymphoma group 2249 gm., as against 1015 gm. for those from splenic anemia cases, and yet the former diseases only rarely cause hematemesis. The same may be said for the large malarial

spleens and those of kala-azar and the leukemias. Furthermore, removal of the spleen does not always stop the bleeding.

As to portal cirrhosis of the liver, it must be admitted that this is sufficient cause and that it may be operative in cases that have advanced to the stage of Banti's disease. But long before this complication has developed gastric hemorrhage occurs, as in our whole series, and so some other factor must be invoked. Likewise, thrombosis of the portal vein is a possible explanation, but it has not been described in many of the cases coming to autopsy.

Splenic vein thrombosis is next suggested and this has been described in a number of cases, notably by Dock and Warthin<sup>7</sup> and later by Warthin<sup>8</sup> and by Rolleston.<sup>9</sup> Such a lesion would account for a damming back of blood into the tributaries of the splenic vein, including the gastric ones, and seems a more reasonable explanation. The chief practical objection to it is that such splenic vein obstruction has been so rarely described, although suggested twenty-eight years ago. This will be referred to again.

Finally, Mr. Lieberman gives, as a suggested cause for the gastric varices, an increased blood-supply to the stomach along with that to the spleen. Pfeiffer<sup>10</sup> has suggested this, and in the report of a case stated that the vasa brevia were large and thin walled. He gives, however, no exact explanation for this enlargement of the arterial branches supplying the stomach and for the increased blood-supply to the stomach. Neither, so far as I can determine, has anyone else attempted to explain it.

Thus it is seen that no very satisfying explanation, applicable to all the cases and having its origin in the nature of the disease itself, is available in the literature. In an attempt to link up the gastric varices more directly with the pathologic lesions in the spleen a very simple explanation has occurred to me. I present it merely as a theory for your consideration and as the basis on which I am planning some investigation.

It is, that the gastric varices may be dependent primarily upon an excessive supply of blood through the splenic artery and its branches, and not, as commonly supposed, upon an interference with the exit of blood from the gastric vessels through

the splenic and other veins of the portal system. Such an increased entrance of blood might conceivably result from two factors that are inherent in the nature of the splenic disease. The first of these is the shunting of a disproportionate amount of the splenic arterial blood into its gastric branches because of partial obstruction to its flow through the spleen; and the second, the sympathetic engorgement of the gastric vessels incident to a greatly increased blood-supply to the diseased spleen.

The essential lesion of the spleen in splenic anemia is a fibrosis with particular involvement of the capsule, the trabeculae, and the reticulum generally. The branches of the splenic artery travel deep in the trabeculae and by various routes send blood throughout the substance of the gland to be collected again into small veins at the edges of the trabeculae. Not infrequently these vessels have been found to show fibrosis and various degenerative changes leading to narrowing of their lumina. Doubtless, in addition, the fibrosis throughout the pulp of the gland offers further obstruction to the passage of blood. In the spleen of our Case I (Table II), a boy of eight years, Dr. Herbert Fox found marked calcareous change in the small blood-vessel walls and a distinct narrowing of the lumina. Much other evidence for such vascular changes in the spleen may be found in the literature, but this is sufficient to indicate the basis for my suspicion that vascular obstruction occurs.

If this be granted, one may think of the spleen in this disease producing an interference with its own circulation just as the liver produces a partial obstruction to the portal circulation in cases of periportal cirrhosis. In the latter disease the portal blood accumulates in the various tributaries to the portal vein and by its increased pressure gives rise to the varices which are well recognized. In the case of the spleen such obstruction would lead to a tendency for the blood to accumulate, also with an increased pressure, in the splenic artery. Under such circumstances it is conceivable that, as a compensatory mechanism, either the artery walls would dilate or the blood would escape by other channels. Being an artery, however, with resistant walls, marked dilatation, such as occurs in veins, would not

develop readily. On the other hand, accessory channels for escape of the excess blood exist in the lateral branches of the splenic artery, the largest ones of which go to the stomach. Passing out through these, under increased pressure and at an accelerated speed, the blood might produce, first, some enlargement of the subdivisions of these branches, especially the capillaries and, finally, on account of their thinner walls, even greater dilatations of the distal gastric veins. Thus I conceive of the gastric varices in splenic anemia resulting from active congestion, the increased blood-supply coming through the left gastro-epiploic and vasa brevia branches of the splenic artery.

Lesions similar to those described as occurring in the small vessels of the spleen have been described in the splenic vein, as previously referred to. Such processes may have the same origin and would lead to the same obstruction to the splenic circulation, and so finally to the same gastric hyperemia. But, in addition, by obstructing the return circulation from the stomach through the splenic venules would act in still another way to bring about gastric varices.

If we think of the same process extending further, from the vessels of the spleen out along the splenic vein and ultimately to the portal vein and its radicles in the liver, we may have the explanation for the hepatic cirrhosis that frequently complicates splenic anemia and produces Banti's disease.

The objection to the theory that obstruction to an artery does not commonly lead to dilatation of the proximal portion of it and of its proximal branches may be raised; and it may be pointed out that ligation of the splenic artery in splenectomy for other diseases of the spleen does not produce gastric hemorrhage. It should be remembered, however, that the vascular changes under consideration take place while the spleen is still present and before the artery is completely occluded. Furthermore, the spleen physiologically presents transient increases in size due to active congestion, and its periodic demands for an increased blood-content may persist even after fibrosis makes such congestion impossible. This may constitute a factor not present in the partial or complete obstruction of arteries generally, and

one that tends, at least irregularly, to keep the splenic artery in splenic anemia overfilled with blood.

In addition, and as a second factor in the engorgement of the gastric branches of the splenic artery, one may think of the possibility of a sympathetic increase of blood to the stomach along with that to the spleen. Both having the same arterial supply, both may become engorged together. This is frequently seen in other adjacent structures of the body.

Neither of these factors can be said to rest upon incontrovertible evidence, but it is believed that they are subject to proof by experimental methods and such investigation is planned.

If obstruction to the circulation through the spleen in cases of splenic anemia can be demonstrated and the existence of the gastric varices so explained, one must still explain why gastric hemorrhage occurs after splenectomy in this disease and not after splenectomy for other splenic conditions. The explanation would seem to be simply that varices once developed persist so long as the arterial supply remains unchanged. It may be suggested, however, that ligation of the gastric branches of the splenic artery or of the artery proximal to these branches at operation might relieve the pressure in the varices and bring about cure.

This projected theory in explanation of the gastric hemorrhages of splenic anemia, then, implies a primary disease of the spleen of cirrhotic nature, leading to obstruction of the circulation through the spleen and, in consequence, to the shunting of an increased amount of arterial blood into the gastric vessels. This increased blood-supply to the stomach is probably sufficient to account for the varices in the stomach, lower esophagus, and the gastric omenta. Under such circumstances various transient increases in blood-pressure or direct trauma may produce rupture of a vein wall and profuse gastric hemorrhage.

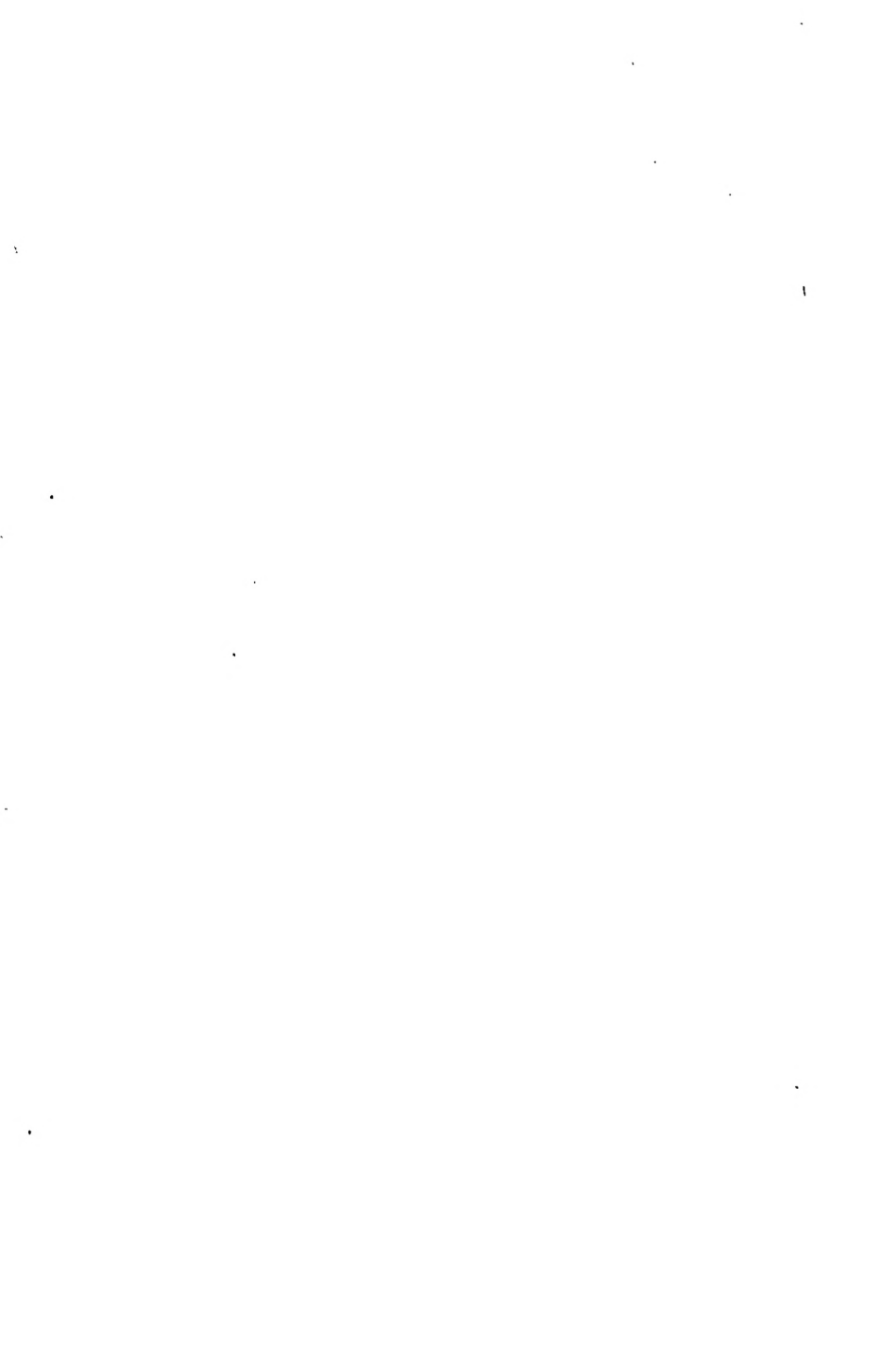
Such a theory at least deserves consideration since it has its origin in the nature of the disease itself, is applicable to all the cases, explains the hemorrhage after splenectomy (when the artery is completely obstructed by ligature) as well as beforehand, and suggests a surgical procedure (ligation of the splenic

artery proximal to its gastric branches) that may overcome the tendency to gastric hemorrhage.

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### THE RÔLE OF THE PROSTATE GLAND IN THE CAUSATION OF REMOTE FOCAL INFECTIVE SYMPTOMS. A DISCUSSION OF THE ETIOLOGY, PATHOLOGY, DIAGNOSIS, TREATMENT, AND PROGNOSIS OF SUCH INFECTIONS.

OF all of the newer concepts of modern medicine perhaps none have been of greater importance than have those based upon accumulating knowledge regarding the far-reaching, and often bizarre, systemic conditions resulting from the presence of limited areas of infection. There is perhaps no special division of medicine that can disregard these influences. The surgeon constantly is called upon to decide whether the pathologic lesion which he sees is a primary condition or is secondary to absorption from some far distant focus of infection. The internist, perhaps, oftener than he, must look far beyond the result to find the cause in some such eradicable focus. The orthopedist, oculist, aurist, neurologist, gynecologist, gastroenterologist, in fact, all of us, often must search far afield if we would be correct in our diagnoses and be of most service in producing cure.

So much to the forefront have these searches for foci of infection stepped in recent years that at times the pendulum has swung so far as to bring discredit. It is only natural that the dramatic cures occurring at times, following the extraction of a tooth or the removal of infected tonsils, should carry us too far forward on the wave of enthusiasm they are sure to engender. Such is the history of almost every discovery of importance, and in its evil there fortunately is a soul of good in

that it more quickly causes us to reach the saner ground between extremes. For instance, though we may deplore the fact that countless perfectly good teeth fell before this wave of enthusiasm, we probably learned more from the suddenness of this great sacrifice and its failures than we should have learned had the tide been a deal more gradual and sluggish. And now we have paused to consider wherein we have erred. We no longer sacrifice teeth as we once did, nor do we overlook infected tonsils because they may be "buried." We study sinuses, gall-bladders, and gastro-intestinal tracts, and then, because the patient states he has never had an attack of gonorrhea, we commonly acquit the prostate gland without study. And because of this acquittal our patient often fails to reach complete cure.

For many years there has been a rather general impression that the prostate gland only became infected in those individuals who had been the victims of gonorrhea. While it is true that there is such a previous history obtained from most individuals presenting an infection of this gland, it is equally true that a large proportion of such prostatic infections have nothing whatever to do with gonorrhea past or present. Further, it is true that an enormous percentage of males presenting infected teeth and tonsils also have infected prostates. So true is this that the male focal infective triad might be said to be teeth, tonsils, and prostate gland. One must not, however, fall into the rather common habit of excluding the patient and thinking only of the demonstrable focus of infection. Not only is there a deeper reason why patients have such infective areas, beyond the fact that bacteria are present, but there apparently are reasons inherent to the patient that act as determining factors in the development of their remote symptoms or lesions. One cannot sensibly view the work of Ralph Pemberton and his co-workers and fail to see that, in the larger picture, the individual focus often plays but a minor rôle; that there are individuals in whom a perverted physiology, that seems in no sense due to the infected focus, gives the lowered resistance that allows the focus to develop and remain active; individuals in whose cure a restoration to or near the normal physiology is the prime

factor, and in whom the eradication of demonstrable foci may take a place of secondary importance. Thus, it shall be seen, that though in the present discussion we are considering the prostate gland, we are in no sense unmindful of that larger picture in which the patient must be considered as one who, among other difficulties, may have an infected gland, rather than an infected prostate gland, in which a patient may be more or less remotely interested.

And yet, did we not vision this larger picture, our clinical experiences with the gland should soon reveal to us the fact that we cannot restrict our field so closely that we gloss over the very intimate association between infections of this gland and other distant foci. This close association has not been sufficiently stressed in the past and there is great need that it should be understood. We must discard our older beliefs and adopt views more in conformity with our constant clinical and pathologic observations.

It has been put forth that at least 35 per cent. of all adult males have infected prostate glands. Such a figure seems well within the realms of fact and, being so, it opens a number of interesting lines of etiologic thought. The well-known rôle of the gonococcus in "preparing the soil," so that other bacteria may continue the infection thus started, makes it rather simple to understand those prostatic infections that justly may be classified as postgonorrheal. On the other hand, no such simplicity obtains in the understanding of that large group that cannot be explained on such grounds. The question, "How and why does the non-gonorrheal prostate become infected?" has received an assortment of answers. Some would place upon the lymphatics the responsibility, others would urge infection by continuity of surface along the urethra, and still others would dismiss both of these in favor of the blood-stream. Certainly the latter seems to carry more anatomic and clinical weight.

The rather constant association of infections of the teeth or tonsils and the prostate in these individuals is sure to engender the belief that the prostate is secondarily infected by bacteria brought to it by the blood-stream from some other

focus. One can recite a number of clinical observations to bear out such an etiologic conception. The fact that it rarely is possible to render such a prostate permanently free of infection so long as the apparently causal focus persists in teeth or tonsils, and that after its removal success commonly attends such efforts, is a strong argument for the thought. It would be possible, did space permit, to cite many such instances. So common are they that it should be the rule to remove, if possible, all distant foci of infection before embarking upon the more tedious and prolonged course of treatment required to eradicate prostatic infections.

A most striking instance of the close association of these various infective foci was that of a patient who, because of a slight nocturnal frequency of urination, had presented himself for prostatic study six times within a year. Each time the prostatic secretion had been absolutely normal. Some weeks after the sixth study he had experienced an acute inflammation of one tonsil. When studied again six weeks after this event his prostatic secretion contained countless large slugs of pus, while the gland had become acutely tender and decidedly enlarged.

While it would be interesting to pursue these phases of the subject much further, it would be better, perhaps, to pass on to the pathologic processes in the gland itself, by what means we may determine their presence and how best to treat them.

It is not possible, as a rule, to differentiate clinically between the types of prostatitis that we pathologically classify as follicular and interstitial. In fact, it is questionable if either process ever exists alone. Nor need we include in the present discussion the glands that show definite abscess formation. Though the prostates that are infected may differ greatly in size, contour, and consistency, we are mainly concerned with the microscopic character of their secretions. We should bear in mind that the nodulated prostate may be, and usually is, either tuberculous or malignant, and that the smooth gland of stony hardness usually is carcinomatous. There is, however, a type of prostate that is extremely sensitive to any digital manipulation, even gentle

pressure causes acute pain and any form of rough manipulation causes long-continued pain. Careful palpation of these prostates usually reveals that they are not so smooth as is usually the case, but impart to the finger the sensation of having small indurated areas in them or, at times, very small nodules that render the gland surface definitely irregular. Singularly enough,

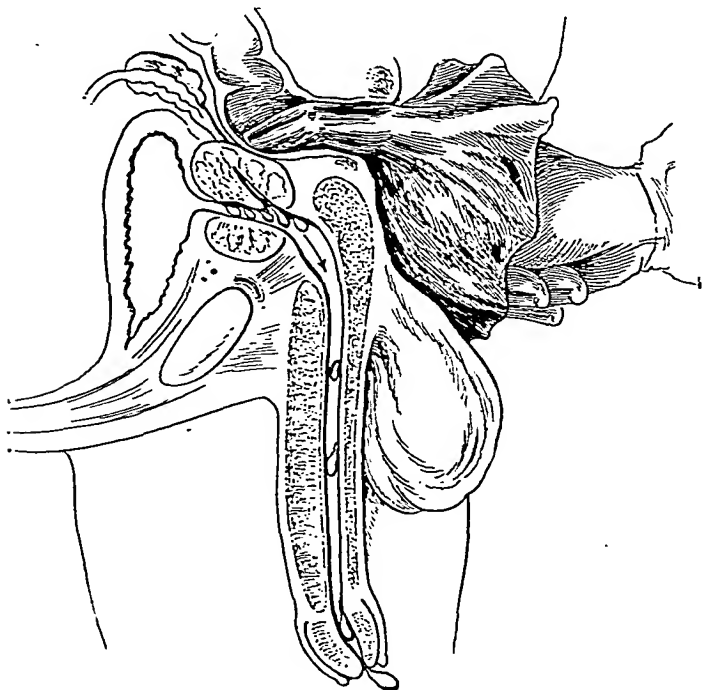
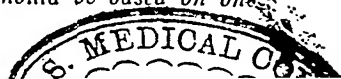


Fig. 167.—Method of obtaining the prostatic fluid for microscopic study. Note the single gloved finger with the cape for the protection of the hand.

this type of gland is more commonly encountered in those individuals who are the victims of chronic arthritis with much deformity, and even the gentlest stroking of the gland causes a marked increase in all of the distant symptoms for varying periods of time.

*It is not possible by palpation alone to say that the prostate gland is normal. Such an opinion only should be based on one*



or more studies of the expressed prostatic secretion. For this reason, one not only should understand the method of obtaining the secretion, but should have a knowledge of its microscopic appearance.

To obtain the prostatic secretion the patient should bend well forward, as in Fig. 167, and the gloved finger, well lubricated, should be passed slowly through the anal sphincter. The lateral lobes of the prostate should be stroked from above downward parallel to the urethra, after which the tip of the finger

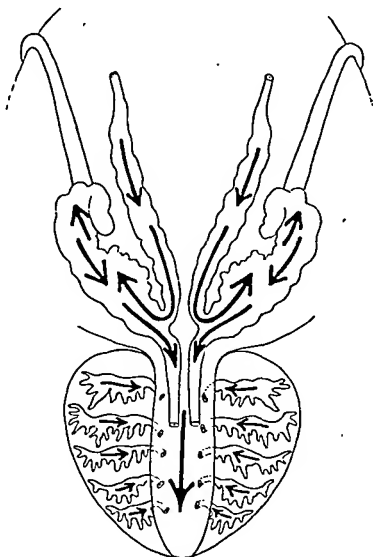


Fig. 168.—Diagrammatic outline of the prostate gland, seminal vesicles and ampullæ to illustrate the normal directions of their fluids.

should be carried far up in the midline and brought somewhat firmly down to the apex of the prostate (Fig. 168). This forces the prostatic secretion into the posterior urethra and thence through the external sphincter into the anterior urethra. If the secretion does not appear at the meatus, slight stripping along the perineum generally will cause it to drop from the urethral openings. Should it be desired to obtain the contents of the seminal vesicles it is necessary to strip them from above downward as is shown in Fig. 170.

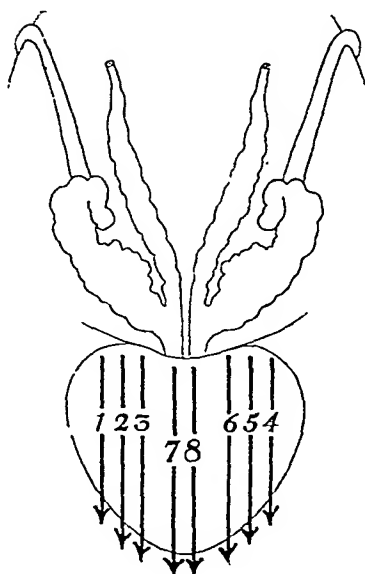


Fig. 169.—Direction of the stroking of the prostate gland. By leaving the midline strokes until last the discomfort is reduced to minimum and is at the end of the treatment.

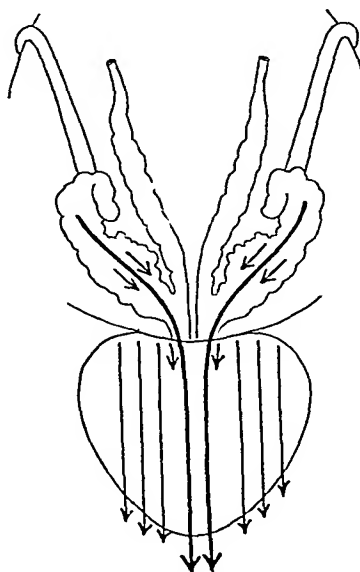


Fig. 170.—Prostatic massage and stripping of the seminal vesicles.  
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Having obtained a drop of the secretion upon a glass slide and overlaid it with a cover-glass, it should be examined in the fresh condition under the 1/6-inch objective. Normally the prostatic secretion may show from two to five polymorphonuclear leukocytes to the field. A secretion exhibiting a greater number evidences infection. It should not be forgotten that some portions of the prostate may be normal while others are infected.

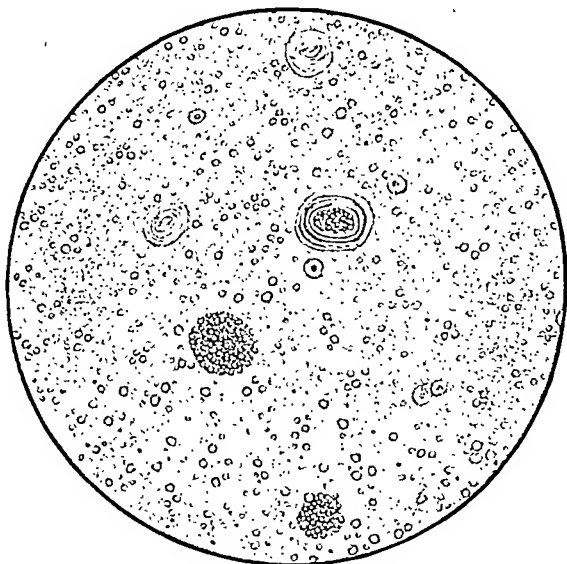


Fig. 171.—The microscopic appearance of normal prostatic secretion. The laminated bodies are corpora amylacea. The other large cells are prostatic granule cells. The next smaller are polymorphonuclear leukocytes in normal numbers. The remainder of the field is studded with lecithin bodies which are characteristic of this secretion.

For this reason, one may obtain a normal secretion only to find at a later study a large amount of pus. So frequently does this occur that a second study is a wise procedure before pronouncing the gland normal. In Figs. 171–175 are depicted microscopic appearances of secretions from the normal, suspicious, and definitely infected prostates. As each bears its descriptive legend there is no need of further description of them here.

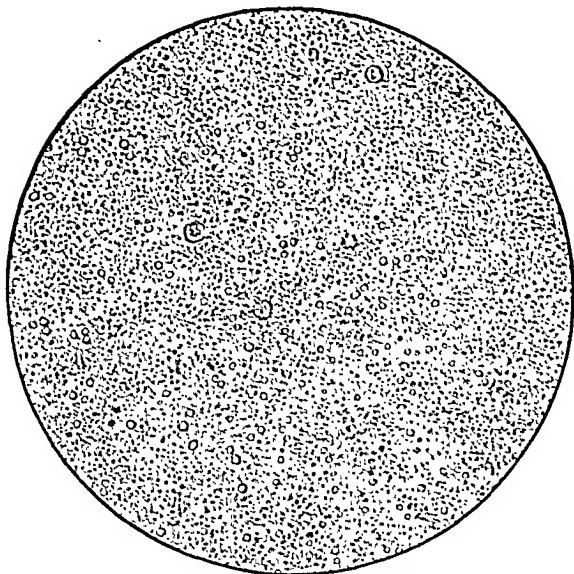


Fig. 172.—Prostatic secretion composed almost entirely of granular débris. A restudy within a few days generally reveals a large amount of pus.

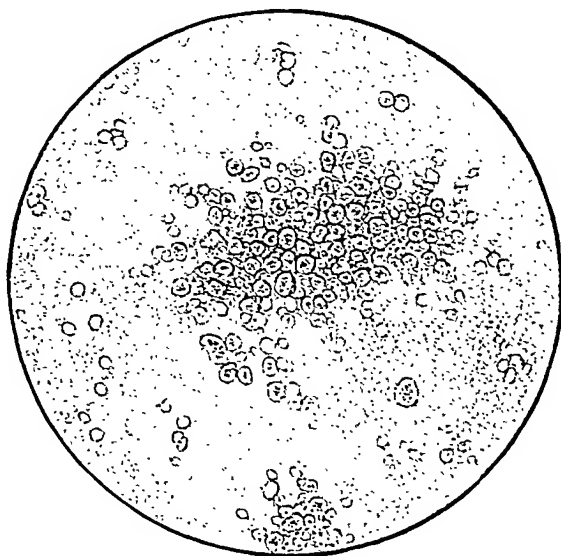


Fig. 173.—Prostatic secretion of a poorly draining infected gland. The scarcity of lecithin bodies in such secretions is very striking. As the leukocytes decrease in number these increase.

Turning to the question of treatment it is well to accentuate again the wisdom of attention to other distant infective foci. So often it is the experience to have the prostatic evidences of infection clear up, and then repeatedly recur until the teeth or tonsils are rendered free of infection, that it is wise to have these attended to first if possible. At times no improvement whatever can be made in the prostatic infection so long as other foci are present. Viewing the gland in cross-section, as

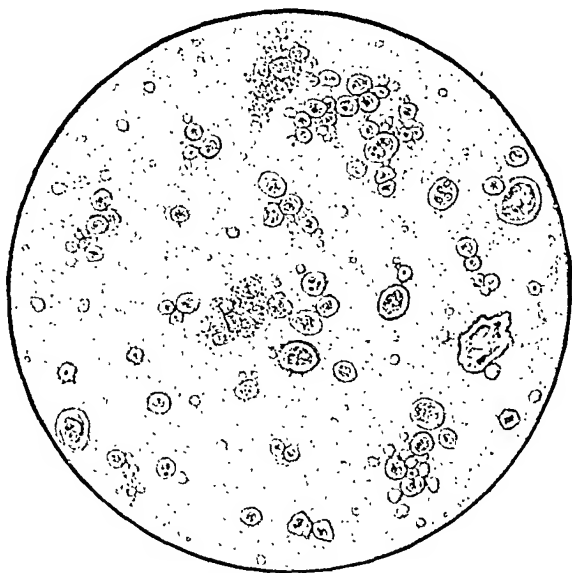


Fig. 174.—A prostatic secretion showing a slight tendency toward clumping of the leukocytes. Such a secretion is commonly seen and bespeaks poor prostatic drainage. It likewise is an intermediate picture evidencing improved drainage where previously there had been large clumps

we do in Fig. 176, one is prone to wonder how a prostate ever does get well, once it has become infected. Obviously, cure is due to several factors, the most important of which is the permanent establishment of better follicular drainage, for infection rarely persists where drainage is adequate. Each prostatic follicle must drain a comparatively large expanse of mucosal surface through a very tiny channel. This channel empties

into a tube, the posterior urethra, which is in the more or less tonic grasp of its own circular muscular fibers. Consequently, in order to establish good drainage, the follicular channel must be patulous, the muscle-fibers of the gland itself must be active, and there must be an active circulation of blood instead of a chronic congestion.

Experience has shown that our one most valuable means of restoring the infected prostate to normal is gentle, systematic,

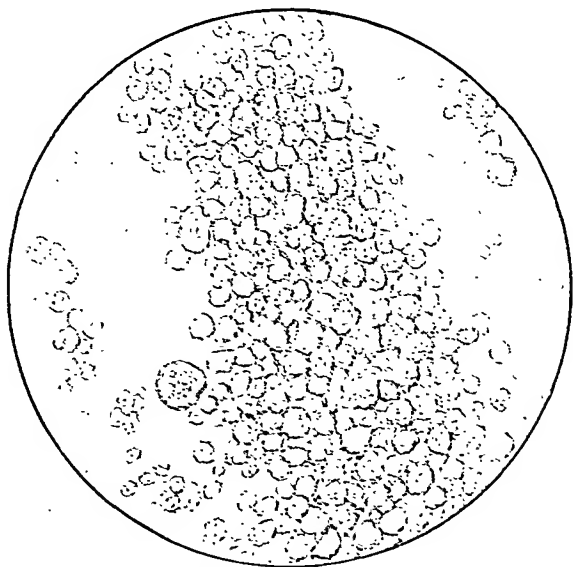


Fig. 175.—Prostatic secretion from a badly infected, non-draining gland. The leukocytes are closely packed, old, and on the verge of disintegration. Lecithin bodies are almost absent.

digital massage. Such treatments should be carried out with judgment, for the degree of tolerance of each individual prostate to digital manipulation is a rule to itself. Consequently one does well to start his course of treatment with due regard to these variations, and only to apply firm pressures to the gland when he has proved it safe. As a general rule it can be said that the pressure that causes great pain to the patient is too great for the given prostate. In judging this, however, one must

make allowances at times for the patient's apprehension. Massage should not be carried out oftener than every three or four days. Treatments spaced at greater intervals rarely, if ever, produce cure, and, given at shorter intervals, they commonly cause an acute inflammatory reaction in the gland.

If there is no improvement in the local condition after six weeks of treatment there usually is some other urogenital pathology that must be removed before cure can be obtained.

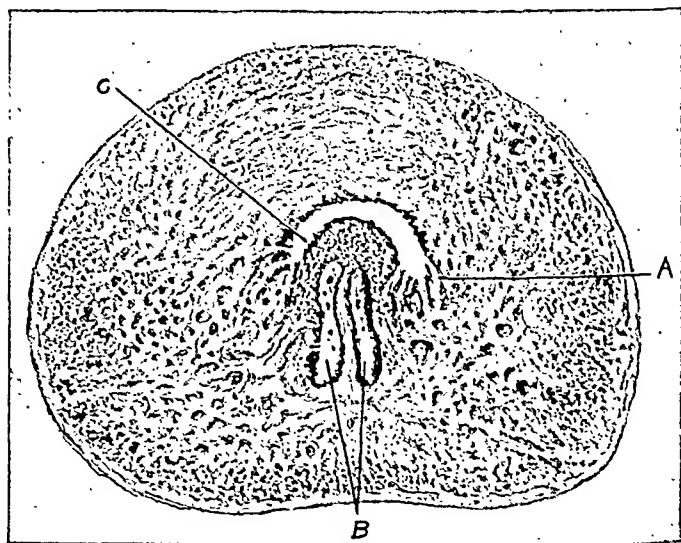


Fig. 176.—Cross-section of the prostate gland at the level of the verumontanum: A, Ducts of the prostatic acini; B, ejaculatory ducts; C, posterior urethra.

It is further safe to say that if the distant symptoms of toxic absorption have not greatly improved or entirely disappeared in that time, there is either a perverted physiology or another focus of infection elsewhere in the body, and the prostate is either not the true cause of the symptoms or is only partly so.

In about 50 per cent. of those patients who have distant symptoms as the sole result of a prostatic infection there occurs a marked increase in these symptoms in about eight hours

after the first massage, followed in from twelve to twenty-four hours by a decided improvement for a day or more. These reactions decrease in severity after subsequent treatments and finally fail to occur.

While there is some difference of opinion among urologists regarding how long such treatments should be continued, the more widely held one is that, if there is still pus in the prostatic secretion after about three months of treatment, twice a week, the patient should have a rest from treatment of from six to eight weeks. Usually, providing there are no other foci, he will be found better after this rest and will respond rather quickly to a second course of like treatments.

Regarding the wisdom of accompanying the massage with intravesical irrigations of some bactericide there likewise is some difference of opinion. If there has been a recent gonorrhea or there is an accompanying cystitis it is wisest to irrigate, leave some fluid in the bladder, and have the patient void it after the massage. If, on the other hand, neither of these conditions maintain, it seems equally safe to have the patient retain his urine for some time prior to the massage and then void it to flush out the expressed purulent secretion. Not only is it safe in this latter class of patients, but they much prefer such a method.

The application of heat to tender or greatly congested glands is beneficial. There is little reason to believe that autogenous vaccines hasten recovery. In fact, observation of a series of cases with and without the use of vaccines has left the writer with the conviction that they at times markedly retard cure.

Regarding the possibility of causing the entire disappearance of pus from most of these prostates there is, in many quarters, considerable skepticism. Unquestionably many such failures can be attributed to the fact that prostatic massage is often roughly carried out. Others are due to irregular treatments, too frequent treatments, or improper methods. Many are due to the fact that the perverted systemic physiology has received no attention or that the causal but distant focus still persists. A few are to be attributed to the fact that the gland has been so badly dam-

aged as to preclude its restoration to anything approaching normal. There have developed a number of thick-walled cavities that cannot collapse. In such cases there usually is a cloudy or hazy first glass and, at times, second glass of urine. In them a clear urine means poor drainage with, possibly, systemic symptoms and urges the wisdom of a course of prostatic massage. Such patients feel best when the urine looks worst.

### SUMMARY

1. The prostate gland is infected in at least 35 per cent. of all adult males.

2. Next to the teeth and tonsils it is the focus of infection causing the greatest number of systemic toxic absorptive symptoms.

3. Most infected prostates can be considered to be the result of a past gonorrhea, though the gonococcus has long since disappeared from the field.

4. A surprisingly large number of individuals who have never had gonorrhea have infected prostate glands.

5. The association of other foci of infection, particularly in the teeth or tonsils, is far too great to be attributed to coincidence.

6. Unquestionably these latter are commonly the primary causes of prostatic infection.

7. It often is not possible to clear up the prostatic pathology until these foci have been removed.

8. Though these distant foci are streptococcic, those in the prostate frequently are staphylococcic.

9. Such being the case brings up the interesting question of why these secondary infections should be continued by other bacteria in what is evidently a blood-borne infection in many cases.

10. The question of perverted physiology from one cause or another greatly broadens the field, and in it apparently lies the explanation of much that now is so poorly understood.

11. The reason for the chronicity of prostatic infections rests largely in the poor drainage of the gland follicles.

12. Our best means of producing cure is through the estab-

lishment of good prostatic drainage by means of gentle prostatic massage.

13. If the distant symptoms of toxic absorption are not greatly improved within one month of such treatments given twice a week, the prostatic infection is not the sole cause of them.

14. If the evidences of infection in the gland are not reduced within six weeks there is some other urogenital pathology retarding cure.

15. If there is still pus in the prostatic secretion at the end of three months the patient should be rested from treatment for six to eight weeks.

16. Autogenous vaccines at times seem to aid, but they are usually quite disappointing.

17. Treatments given at shorter intervals than three days commonly cause an acute inflammatory reaction, and given a week apart, they seldom produce cure.

18. There are some prostatic infections in which the gland is so badly damaged that it cannot be rendered free of pus.

19. Such patients feel best when the urine looks worst. In them a clear urine commonly urges the wisdom of prostatic massage to promote drainage.





# CLINIC OF DR. FREDERICK L. HARTMANN

## THE LANKENAU HOSPITAL

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### HYPOGLYCEMIA

ESSENTIAL or idiopathic hypoglycemia is a new clinical entity. Other terms given to it are "hyperinsulinism" and "glycopenia."

The condition with its peculiar and varied symptoms has only been recognized within the past decade, and then mainly through the discovery of new microchemical methods that enable one to determine blood-sugar concentrations. Insulin therapy with its hypoglycemic shock has served as an added factor in studying the new disease.

The symptomatology is varied, but characteristic. It manifests itself in attacks. During the interval the patient may be in apparent excellent health, but during the attack the phenomena produced by overdosages of insulin make their appearance.

Characteristically the attack comes on several hours after meals, as during the night or early morning before breakfast. Physical labor or exercise between meals will shorten the intervals.

A sensation of weakness associated with a feeling of hunger is usually the first complaint. Then follows a feeling of anxiousness and a sensation of inward trembling. This latter begins in the extremities and passes on to the body. Excitability and slight emotional disturbances are next seen. Sweating, tachycardia, blurring of vision, and diplopia develop. Incoördination is seen as the patient attempts to drink or to rub his hands over his eyes in an endeavor to clear his vision. Motor aphasia, tremors, mental confusion, and disorientation are next in order.

Then clonic convulsive movements not unlike epilepsy set in. They gradually subside and the patient passes into a state of coma unless carbohydrate is given to abort the attack. However, not all attacks will proceed to coma if no carbohydrate is given, but may pass off at any stage depending upon some autonomic mechanism that releases stored-up glycogen to raise the blood-sugar concentration.

The causative factor of this train of symptoms is the lowered blood-sugar concentration. That in itself is but a laboratory finding and the true pathologic or pathophysiologic condition underlying it must still be found.

Essential hypoglycemia was referred to above as a disease entity. This is erroneous. It is only a symptom-complex, varying in intensity, associated with a lowered blood-sugar concentration due to one of several causes. Further investigations will bring out definite causative factors. Just as asthma is found as a complication in cardiac, renal, or allergic patients, so no doubt will hypoglycemia be found associated with certain endocrine disturbances, or liver and pancreatic involvement.

Experimental hypoglycemia has been produced in animals by means of toxic substances and by surgical procedures on certain organs, especially the liver, pancreas, and adrenals.

Chemicals that have a selective toxic action on the liver, such as hydrazin, chloroform, and phosphorus, cause hypoglycemia with a marked decrease in the glycogen content of the liver.<sup>1</sup>

Ligating the vessels of the liver, or removal of part or the whole liver, causes marked and fatal hypoglycemia.<sup>2</sup>

Alpern and Besuglow,<sup>3</sup> in their experiments on ligation of the pancreatic duct or the application of a mass-ligature to a part of the pancreas, found that a hyperfunction of the islands of Langerhans was evidenced by changes in carbohydrate, fat, and mineral metabolism. This was identical with the changes observed after administration of insulin.

The relation of the adrenals to carbohydrate metabolism is still under dispute. Some observers (Porges<sup>4</sup>) claim that the removal of these glands causes hypoglycemia. Other observers have failed to substantiate these findings. It has been found,

however, that rabbits were more sensitive to insulin after adrenalectomy than before the removal of the adrenals.

Low blood-sugar concentrations are found associated with many diseases involving different parts of the body and doubtless are causative of the weakness and asthenia that is common to them all. Jonas<sup>5</sup> in his excellent paper on hypoglycemia covered the literature up to his time. I shall briefly enumerate these associated diseases:

1. Conditions involving the endocrine glands, such as myxedema, cretinism, hypopituitarism, and Addison's disease.
2. Progressive muscular dystrophy.<sup>6</sup>
3. Complete physical exhaustion following prolonged strenuous exercise, as in Marathon racing.<sup>7</sup>
4. Following subtotal thyroidectomy.<sup>8</sup>

In these conditions the hypoglycemia was mild. Recently Pribram<sup>9</sup> reported several cases with what he termed "chronic glycopenia." They all showed weakness, chronic constipation, headache, and vomiting. All had low blood-sugars. They were all subjectively and objectively improved when their blood-sugar levels were raised to normal.

Joslin<sup>10</sup> and Woodyatt<sup>11</sup> report some severe cases of hypoglycemia, several of which were fatal. These occurred in diabetics. They had been on undernutrition diets and had never received any insulin. In all the cases there was a sudden marked loss in weight preceding the hypoglycemia. They died in coma or in convulsions.

Harris<sup>12</sup> reports several cases that complained of extreme weakness and fatigue an hour before meals. If nourishment was not obtained at that time, they felt that they could not survive. Examination of the blood during these attacks showed a blood-sugar concentration of 0.060 to 0.07. These patients were also potential diabetics. They had never received any insulin.

Harris advances the thought that hyperactivity of the islands of Langerhans causes the sensation of hunger for carbohydrates. There is then an increase in weight. Following this, the isles become exhausted and a hypo-insulinism or diabetes results.

Mild cases of hypoglycemia in hepatic disease have been reported by Cammidge.<sup>13</sup>

Wilder *et al*<sup>14</sup> report a most interesting case of carcinoma of the pancreas. The primary growth originated in the islands. There was an associated hyperinsulinism and hypoglycemia. The primary growth and also its metastases gave a high insulin content, thus showing an instance where the cancer cell had retained the function of the parent cell.

This case was one of extreme hypoglycemia similar to the one I shall cite later. The authors refer to the cases reported by Jonas, among which was my case given before the Philadelphia Physiologic Society in March, 1924.

Twenty cases of adenomata of the islands of Langerhans are recorded in the literature, but association of these with hypoglycemia is not made.

McClenahan reported a case of adenoma of the islands of the pancreas with hypoglycemia before the Philadelphia Pathologic Society during April, 1928. The patient died in coma with blood-sugar concentration of 0.036 mg. per 100 c.c. blood. This low blood-sugar was found in spite of glucose by lavage, bowel, and vein. The sugar content of the blood for the three days preceding death had been 0.040, 0.045, and 0.040. The sugar content of the spinal fluid was also found very low. At autopsy an encapsulated tumor was found in the pancreas. This tumor was composed of cells similar in structure and arrangement to those of the islands of Langerhans. Associated with the growth was a generalized hyperplasia of the islands throughout the pancreas. There was no evidence of metastasis. The glycogen content of the liver was normal.

Unfortunately no biologic test was made of an extract of the tumor tissue to ascertain its insulin content.

A similar case has just been reported by Thalheimer and Murphy.<sup>15</sup> There was an isolated nodule in the pancreas composed of islet cells, but apparently undergoing malignant change. No evidence of metastases was found however.

## CASE REPORT

Mr. W. S., aged forty-three years, was admitted to the medical ward of The Lankenau Hospital on November 13, 1923.

His chief complaint was: "If I do not eat every two hours I have a spell and lose my mind."

He had enjoyed perfect health up to four years before. At that time he was working in a saw-mill when he began to experience the sensation of being unable to let go of logs as he placed them on the shuttle for sawing. Fearing injury to himself, he secured a new occupation as laborer. A short time after this he began having the symptoms of his present illness.

A sensation of extreme weakness compelled him to rest between meals. During these times he often developed diplopia. He would see two trolleys or two automobiles approaching him when there was but one. He noticed

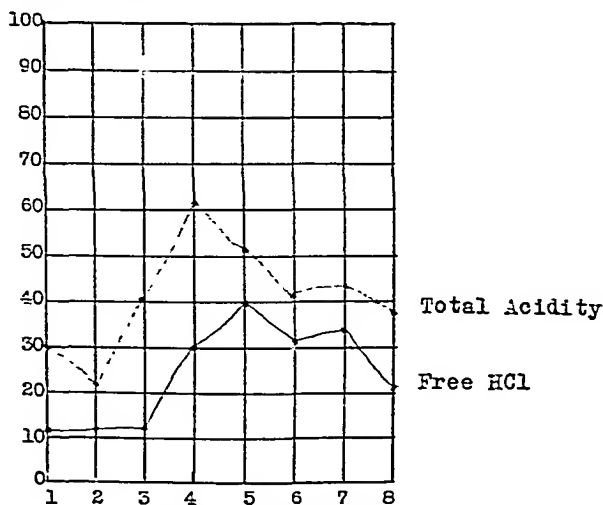


Fig. 177.—Fractional test-meal.

that he could resume his work more quickly if he ate a sandwich during the rest period. The attacks of weakness persisted and increased in intensity so that he had to eat every two hours.

If he was unable to obtain food, the sensation of weakness became extreme and was followed by loss of power to stand. He would go into a convulsion and "lose his mind" (meaning loss of consciousness). On one occasion he had an attack on the street and was taken to the police station as a "drunk."

For the past year the attacks have occurred during the night. His wife would find him semidelirious and tossing about in bed. Food always relieved the condition. Since then his wife has regularly fed him every morning at 3 o'clock.

His urinary, gastro-intestinal, cardiac, and respiratory systems were

the past two years. Felt fine between attacks.

The past medical history was entirely negative except for a motorcycle accident five years before. At this time his left groin was injured, the left leg becoming swollen and blue. The condition cleared up quickly.

His father and mother and four brothers and sisters were living and well. No one in the family had a similar condition and there had never been anyone ill with diabetes. His wife was well. Two children had been born, but died in early life of meningitis and pneumonia. His habits were good. Smoked moderately. Denied use of alcohol, but was very fond of sweets.

The physical examination was essentially negative. He was well developed and well nourished. Exposed skin surfaces tanned by the weather. No cyanosis. No jaundice. Scalp showed no scars. There was a slight deflection of the septum to the left. Pupils were equal and regular and reacted to light and accommodation. No weakness of the extra-ocular muscles. No nystagmus. Mouth negative. Many teeth had been extracted. Tongue protruded in midline without tremor. The thyroid was not enlarged. No lymphatic enlargements.

Chest was well developed, but free of hair. The lungs were clear and the heart normal to percussion and auscultation. Abdomen was free of scars. Showed sparse pubic hair. Liver edge palpable at costal margin. No masses or rigidity or tenderness was found. Genitalia normal. The extremities and reflexes were normal. The systolic blood-pressure was 138 and the diastolic 68.

The blood-count showed a hemoglobin of 80; red blood-cells, 3,840,000; white blood-cells, 8300. Polynuclears 63 per cent.; small lymphocytes 31 per cent. Blood-urea nitrogen 21 mg. per 100 c.c. blood. Blood-Wassermann was +1. The urine was negative for sugar and albumin and contained only phosphates. Examination of stool showed it to be alkaline; bile, strongly positive. Microscopically a few fat globules and an occasional muscle remains were found. No starch, ova, or parasites.

The blood-sugar determination was not made until several days after admission because the patient was being given frequent feedings and, frankly speaking, hypoglycemia was not even thought of. The x-ray of the skull showed all sinuses clear. The left frontal sinus was larger than normal and the right frontal sinus below the normal size. The sella turcica was neither eroded nor enlarged. Basal metabolism was normal—46 calories per square meter per hour. The eye-grounds showed slight pallor of the nerve-heads. Vision good. Form-fields were moderately constricted temporally. On the fifth day after admission the patient's food intake was restricted so that a blood-sugar could be taken. It just so happened that the patient was in the midst of one of his attacks at the time the blood was taken. The blood-sugar concentration was  $0.042$  mg. per 100 c.c. blood (Folin-Wu method).

**Clinical Studies.**—The patient was placed on a diet of 3000 calories: carbohydrate 200 gm., protein 100 gm., and fat 200 gm., with the addition of sweetened orange juice should an

attack occur. In spite of this diet the patient would develop attacks. The blood-sugar concentration during these attacks ran 35, 36, 32, 32, 35, and 37.

Patient had been placed on mixed treatment in view of his slightly positive Wassermann. The repeat one week later showed a strong +4, but leutic treatment was continued.

Food was withheld to bring on an attack. Three hours after the last meal the patient complained of feeling weak and was having difficulty in seeing. Blood-sugar was 0.052 mg. per 100 c.c. of blood. His eyes became staring, the face mask-like, with the lower jaw drooping. Saliva ran from the corners of his mouth, the face twitched, and the tongue rolled about in the mouth. The facial muscles were drawn up in choreiform movements with twitching and athetoid movements of fingers and arms and legs. He could not articulate. He simply grunted. His movements then became clonic convulsive in type resembling an epileptiform seizure. There was no loss of sphincter control. Patient was absolutely unconscious. This all occurred within twenty minutes.

Ten minims of adrenalin hydrochlorid 1 : 1000 were now given hypodermically and in ten minutes the patient was feeling comfortable again. His blood-sugar now was 55 mg. During the course of the patient's stay in the hospital adrenalin hydrochlorid in the above amount was given on eleven occasions and always aborted an attack.

Pituitrin in 5-drop doses was tried on two occasions, but without effect. More about this later.

A sugar-tolerance test was made, with the following results (blood-sugar before giving 120 gm. glucose was 0.053 mg.):

Time.	Blood-sugar concentration.	Urine sugar content.
$\frac{1}{2}$ hour.....	0.135	No urine
1 hour.....	0.166	No sugar
2 hours.....	0.216	0.28 per cent.
3 hours.....	0.100	No sugar

Patient was allowed to return to his home on January 8, 1924. His blood-sugar was 0.078 mg. on the morning of leaving.



He had gained 15 pounds in weight. He was advised to carry lump-sugar in his pocket and to take this at the onset of weakness. He was to return after concluding some household affairs.

**Readmission.**—He was readmitted on January 29, 1924. There were no changes and he had kept free of attacks by taking the sugar. Blood-count now showed hemoglobin, 90; red blood-cells, 4,360,000; white blood-cells, 10,200; polymorphonuclears, 56; lymphocytes, 35; large mononuclears, 5; transitionals, 2; eosinophils, 2.

Further studies were made with pituitrin and adrenalin:

	Time.
1/30/24	7.10 A. M.—Attack began
	7.15 A. M.—Blood-sugar 0.039
	7.20 A. M.—Adrenalin, 10 minims
	7.30 A. M.—Blood-sugar, 0.057
2/1/24	10.10 A. M.—Attack began
	10.18 A. M.—Blood-sugar, 0.032
	10.20 A. M.—Adrenalin, 10 minims
	10.35 A. M.—Blood-sugar, 0.081
2/12/28	4.45 P. M.—Attack began
	4.50 P. M.—Blood-sugar, 0.036
	4.55 P. M.—Pituitrin, 10 minims
	5.10 P. M.—Patient slowly coming out of attack
	5.20 P. M.—Blood-sugar, 0.054

Patient was discharged on February 17, 1924. He was placed on mercury and iodids and advised to continue with the lump-sugar.

**Readmission.**—May 1, 1924. Patient returned, having gained 25 pounds since his first admission. He had been able to do little work due to the spells coming on. Rest and sugar always relieves, but not for as long an interval as before. Recently he had developed a cold and felt weaker.

Examination was essentially the same. Blood-pressure: systolic, 135; diastolic, 90. Blood now: Hemoglobin, 85; red blood-cells, 4,960,000; white blood-cells, 17,900. Polymorphonuclears, 63; lymphocytes, 28; large mononuclears, 6; transitionals, 3. Blood-urea 17; Wassermann, negative; urine, negative. Blood-sugar during attacks, 0.025, 0.043, and 0.035. Adrenalin

would still abort attacks. A sugar-tolerance test with 200 gm. glucose was now given:

Time.	Blood-sugar.	Urine sugar content.
7 A. M. ....	74	No sugar
9 A. M. ....	242	2.27
10 A. M. ....	140	1.85
11 A. M. ....	66	No sugar

**Readmission.**—He lived in another state and it was difficult to keep in touch with him. He remained essentially the same, but on October 13, 1924 he was readmitted, complaining of the same attacks plus some slight epigastric distress and sour eructations after meals.

Again physical examination was negative. No masses or areas of tenderness were found. Liver palpable at costal margin. He had now gained 45 pounds in weight since his first admission. Blood-pressure was now 108 systolic and 70 diastolic.

Blood count: Hemoglobin, 90; red blood-cells, 4,300,000; white blood-cells, 8100; polymorphonuclears, 68; lymphocytes, 27; large mononuclears, 5; Wassermann, negative; blood-urea nitrogen, 12; urine, negative.

x-Ray of skull again negative. Gastro-intestinal x-ray report showed the stomach hypertonic with moderate degree of hyperperistalsis. Pyloric end a little high and to the right with the cap slightly flattened. No craters detected. No retention. Remainder of tract was negative.

Blood-sugar during attacks still ranging at same low levels 0.055 and 0.040 mg.

The only point of interest now was the change in the effects of adrenalin. It was not so prompt in its action, and whereas previously it had raised the blood-sugar 20 or more points, it now would cause an elevation of only 10 to 12 points.

The patient was given rest in bed and frequent feedings of a soft diet. The gastric symptoms quickly subsided. He was discharged October 31, 1925 improved, but still having his hypoglycemia of undetermined cause.

Following this last admission all trace of the patient was lost until the summer of 1926. He had grown progressively

weaker and the attacks more severe. Unable to work and with funds exhausted he had been sent by a physician in his home town to a state institution for epileptics, where he was admitted on April 26, 1926, and died on May 9, 1926. No autopsy was performed.

The reply by the superintendent of the institution to my letter of inquiry gives some information as to the mode of death and indicates how closely the attacks in this patient resembled epilepsy. There is no doubt in my mind that the so-called epileptic convulsions were the hypoglycemic attacks.

I will read you the reply as received:

"In acknowledgment of your letter will say that we can give you no history of condition before his admission to our institution, which was on April 26, 1926. He had a convulsion on April 27th, 29th, and 30th, two on May 1st, after which he became exhausted, but he had a convulsion May 2d, another on May 3d and 4th. He failed to recuperate from these convulsions and died of epileptic exhaustion on May 9, 1926."

**Discussion.**—Undoubtedly this was a true case of hyperinsulinism associated with hypoglycemia. The lesion must have been situated in the pancreas and involved mainly the islands of Langerhans. I do not think that it was a case of carcinoma of the islands. The patient had had this condition for a period of over seven years; gained in weight and maintained a normal blood-count. This seems inconceivable with cancer. However, in the case of carcinoma of the islands of Langerhans reported by Wilder and his associates, their patient also gained in weight and likewise showed no outward evidence of malignancy in spite of metastases being present. They assume from the appearance of the primary growth that the cancer had been there for years. On the other hand, the primary growth might have been an adenoma of the islands, which shortly before death had undergone malignant degeneration with metastasis. If this were true, then the patient would not have had time to develop cancer cachexia before his hypoglycemic death.

The action of adrenalin and pituitary extract in aborting the attacks and raising the blood-sugar concentration strongly

suggests the neutralization of insulin action. It is well known that these extracts will bring patients out of hypoglycemic reactions induced by injections of insulin. Also when insulin and adrenalin or pituitary extract are injected together the action of insulin is neutralized.

Furthermore, it can be assumed that the glycogen-storing capacity of the liver must have been normal or at least sufficient. If it had not been, then injections of adrenalin would not have raised the sugar concentration. Experimentally adrenalin has no effect upon the hypoglycemia caused by extirpation of the liver or destruction of the liver-cells by means of hydrazin. In my case as the condition progressed adrenalin did not have the prompt and marked action as at the start. This may have been due to a lowered glycogen content or more likely, as Wilder suggests, to a more complete fixation of the glycogen in the liver-cells by the excessive amounts of insulin present.

This case is also of interest in showing how low the true sugar concentration of the blood can go. Somogyi<sup>16</sup> has shown that the amount of reducing non-sugars in human blood is very uniform: average 27 mg. per 100 c.c. of blood in terms of glucose, as determined by the Shaffer-Hartmann method with the modified reagent. Moreover, it is independent of the blood-sugar level and rises above the normal only in cases of high nitrogen retention. Therefore, deducting the 27 mg. from the low levels in this case of 32 mg., there is only a 7 mg. true reducing sugar in the blood at the height of the attack.

The glucose tolerance tests were of interest in showing that this patient although having hyperinsulinism was also a potential diabetic. The blood-sugar rose to an abnormally high level and sugar was excreted in the urine after the injection of 120 and 200 gm. of glucose.

Many cases of hypoglycemia and hyperinsulinism have heretofore probably been seen and incorrectly diagnosed because since the condition has been recognized many new cases are appearing in the literature. In my case, as an instance, the patient was thought to be suffering from epilepsy and was so diagnosed at death.

To sum up, therefore, the case presented shows all the characteristic symptoms of a patient suffering from hypoglycemia. Blood-sugar concentrations proved this to be the case. The cause for the condition unfortunately is not known, as no necropsy was held. However, from the severity of the symptoms, the clinical findings, and the termination of the case, one causative factor was an excessive amount of insulin in the blood-stream. This may have come from hyperplastic and hyperactive islands of Langerhans, from an adenoma of these isles, or from a carcinoma of the same structures.

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## CLINIC OF DR. HAROLD R. KEELER

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### ENDOCARDITIS ASSOCIATED WITH ARTERIAL THROMBOSIS

EMBOLISM of the visceral blood-vessels is not an uncommon feature in acute or subacute bacterial forms of endocarditis. To discover embolism in the larger blood-vessels of the body is not only a singular, but a spectacular happening. Bull<sup>1</sup> examined more than 6000 necropsy records at Rik's Hospital, Oslo, and found embolism of the extremities occurred fifteen times, fourteen times in the lower extremities and once in the upper. In approximately 200,000 registrations in the Mayo Clinic, 21 cases of circulatory disturbance of the extremities resulting from an obstructing arterial embolus were found. Embolism in the vast majority of cases has its origin from a thrombus or vegetation in a diseased heart, usually the left side of the heart. In a few instances, where a patent foramen ovale is found, a so-called "cross" or "paradoxical" embolism may exist. At times embolism may have as its focus the systemic veins or the intima of arteries—as in endarteritis of the aorta. In acute bacterial endocarditis Clawson<sup>2</sup> found that embolic phenomena of one sort or another existed in 90 per cent. of the cases. In the subacute bacterial endocarditic group 62 per cent. of the cases showed embolism. In not one case of acute rheumatic endocarditis could embolism be found.

The case report which follows is of interest because of: (1) The location of the embolism, (2) the difficulty in diagnosis of the existing endocarditis, prior to the development of embolism, (3) the question of the probable source of infection.

**Case Report.**—F. G., an Italian male, aged thirty-one years, entered the hospital on April 23, 1928, with a chief complaint of pain in his left abdomen, chills, and fever.

He was well until March 25, 1928, when he began to have cramp-like pains in his abdomen. He vomited on several occasions. Vomitus consisted mainly of food particles. He had chills and fever, but was able to continue with his work until March 31st, when he was seized with a sudden, excruciating knife-like pain just below the umbilicus, severe enough to double him up. His physician told him he had gall-bladder trouble. The pain later subsided somewhat and settled in his left loin. It seemed to be aggravated at the time of his chill, which he had two to three times a day. He had eaten no solid food since March 31st. Bowels were constipated. He had no cough or pain in his chest. No dyspnea. No pain in the cardiac region. No palpitation. No dysuria. Occasional nocturia. No hematuria.

**Past Medical History.**—He had never had an attack similar to one described above. Had influenza in 1918. Had several attacks of tonsillitis, the last in February. Never had rheumatism. Had never been told that he had had heart trouble. Never had chorea, diphtheria, or scarlet fever. Neisserian infection in December, 1927.

**Family History.**—Negative.

**Social History.**—Lineman for Philadelphia Rapid Transit Co.

**Physical Examination.**—Temperature on admission, 100.1° F.; pulse, 110; respirations, 24. Blood-pressure, 124/80. He had many gold-capped teeth and marked pyorrhea alveolaris. Pharynx was injected. Tonsils cryptic and injected, and of moderate size. Chest expansion was free and equal on both sides. Percussion note was resonant throughout. Breath-sounds were physiologic. No râles were heard. Heart was not enlarged. Heart-sounds were of good tone and quality. No murmurs were heard. There was no arrhythmia. Aortic second sound was greater than pulmonic second sound.

The abdomen was rigid, especially on left side. There was tenderness in area of Petit's triangle on both sides, more especially on the left. Liver and spleen could not be palpated. The back was held somewhat rigidly. No tenderness was elicited along the spine. There was no tenderness in the kidney regions.

Rectal examination failed to reveal any palpable pathology.

The reflexes were all prompt and active. There were no petechiae on the body or extremities.

Blood-count on admission: Hemoglobin, 88 per cent.; red blood-cells, 4,200,000; white blood-cells, 13,900; polymorphonuclears, 75 per cent.; small lymphocytes, 22 per cent.; large lymphocytes, 2 per cent.; transitionals, 1 per cent. A white-cell count made two days after admission was 9500. On the 26th a spinal puncture was done—20 c.c. of clear spinal fluid removed under normal pressure. Queckenstedt's test was normal. The cell-count was 4 per cubic millimeter. Globulin not increased. Sugar present. The blood Wassermann and spinal fluid Wassermann tests were negative. A smear and culture of the spinal fluid showed no organisms.

Blood was examined for malaria, but no plasmodia were found. Blood

Widal test was negative. Stool examinations were negative. An x-ray examination of the lumbar spine and pelvis was negative, except for spina bifida occulta of the upper sacral segment.

Cystoscopic examination showed a normal bladder. There was normal function in each kidney. No pus in the urine. Pyelogram of the left kidney revealed an intrarenal type pelvis, the kidney itself was negative.

Blood-chemistry analyses were all normal. Blood-culture was negative.

Urinalyses were made daily, and were negative throughout.

The temperature ranged between 100° and 103° F., pulse between 90 and 120, and respirations between 20 and 24, during the first eight days of his stay in the hospital. On two occasions during that time he had normal temperature, pulse, and respirations, lasting over a period of eight to ten hours. Patient's general condition seemed good right along. The fourth day after admission his abdomen was soft, and no tenderness was elicited. There was no splenic enlargement. Appetite was good. On the morning of May 2d, the ninth day after his admission, he was seized with a sudden, severe pain in his back and right leg. The pain in his back soon subsided, but persisted in his leg. Examination at this time showed good movement in his leg, but from the knee down the leg was cold and white. No pulsation was elicited in the dorsalis pedis artery. Sensation of touch was lost from the knee down and he could not feel pin-pricks over the anterior portion of his lower leg, but could feel them on his calf. Scratching on the sole of his foot produced no reflex, but a few moments later he complained of severe burning sensation in the area scratched. The thigh was warm, of normal color, and showed normal sensations. A diagnosis of thrombosis of the popliteal artery was made and he was immediately taken to the operating room. At this time his temperature was 100° F., pulse 114, and respirations 24. Under ether anesthesia the right popliteal artery was exposed, but was found to be non-pulsating. An incision was made in the femoral triangle, and femoral artery was exposed. This artery too was found to be non-pulsating, so an incision was made in the lower abdomen and the common iliac artery was exposed. Pulsation was found just above the division of the common iliac artery, but none in either of its branches. Common iliac artery was opened and an embolic thrombus removed. This thrombus lay across the division of the common iliac artery and extended down into each branch. The artery was closed and pulsation elicited in both branches of the iliac. At this time no pulsation could be found in the femoral artery. A needle was inserted into the artery and blood removed. After patient was returned to ward leg was elevated and heat applied, but circulation never became established below the knee. The next morning (May 3, 1928) patient complained of a severe pain in his left leg. He told his doctor that the same thing had happened on his left side. On examination, found absence of pulsation on dorsalis pedis artery, but definite pulsation in the femoral artery. Diagnosis of thrombosis of the left popliteal artery was made. The left popliteal artery was exposed, a clot found and removed, and for several hours afterward circulation seemed to be established in that leg. By May 5th definite dry gangrene had set in in both legs, necessitating their amputation at the knee-joints. There was no secondary hemorrhage following either the embolec-



tomies or the amputations. Patient died of exhaustion and shock on May 7th. A systolic mitral murmur was heard several days before the patient died, probably hemic in character.



Fig. 178.—Acute bacterial endocarditis. Showing large sessile vegetation on posterior leaflet of mitral valve. Vegetation can be seen not to encroach on the line of closure of the valve.



Fig. 179.—Common iliac artery exposed, showing thrombus. This thrombus had formed after the first embolectomy was done.

At autopsy the only pathologic conditions found were: (1) Vegetative endocarditis; (2) small anemic infarct of the

spleen; and (3) thrombosis of the right common iliac artery. The heart was of normal size and the walls of the cardiac chambers were not thickened. On the posterior mitral valve was found a rather large, single, sessile vegetation. It was not very friable. The vegetation did not reach the line of closure of the valve, and this finding would account for the absence of murmurs. The spleen was only slightly enlarged. Cultures were made at autopsy from blood taken from the heart, from the vegetation on the mitral valve, and from the thrombotic mass in the common iliac artery. They were all found to be negative. All cultures were made in a special hormone broth and on human blood-agar at normal and reduced oxygen tensions.

On microscopic examination of section of mitral valve and wall of heart, these structures were found to be devoid of normal covering, presenting an ulcerated surface covered with a thrombus, in which were scattered groups of cocci as well as a few cocci generally distributed through the whole mass. The cocci were all extracellular. There were no Aschoff bodies in the myocardium. Sections of the liver and the kidney were normal. No emboli were found in glomeruli of kidneys. A small anemic infarct was found in a section of the spleen. The thrombus in the iliac artery was not studied microscopically.

We were here confronted with a patient who complained of a rather vague, non-radiating pain in his left abdomen, chills, and fever. His temperature, as you see, was for the most part remittent in type, although on several occasions he was fever free for a number of hours. It was higher after a chill. He was a well-developed, fairly well-nourished man who did not appear extremely sick. He answered questions fairly intelligently. On physical examination we found his blood-pressure to be normal. Tonsils were cryptic and pillars injected. Heart and lungs were negative. There was no enlargement of liver or spleen. There was some rigidity and tenderness of left abdomen. There was some rigidity of the back.

With chills and fever, and a tendency for the fever to be intermittent in type, we must, of necessity, think of malaria. This diagnosis was temporarily ruled out when no malarial

parasites were found in the blood. An increased leukocyte count, with no increase in the percentage of the large mononuclears, would help us to exclude that possibility.

Hepatic colic may give us so-called Charcot's intermittent fever. There was no tenderness over the liver, no pain in region of the gall-bladder radiating to the right scapula, and no jaundice.

He did not appear prostrated enough to have typhoid fever. He had no headache, no nosebleeds, and no cough. There was no characteristic temperature curve. There was no splenic enlargement. No rose-spots were found on his body. There was no leukopenia. Blood-culture was negative, and his blood-Widal test was negative.

Tuberculosis was excluded because of his negative history, absence of cough, night-sweats, hemoptysis, etc. He had lost no weight. Lungs were found to be normal. Blood-culture showed no tubercle bacilli, although it was not made on a special medium.

Cystoscopic examination, ureteral catheterization, and pyelography of left kidney were all negative for a possible calculus. Urinalyses were negative for blood. The pain, tenderness, and rigidity of the left abdomen warranted this full examination.

Because of the rigidity of the back, a lumbar puncture was performed to exclude cerebrospinal meningitis. The clear spinal fluid, which was found to have a normal cell-count and showed no bacteria on culture and smears, ruled out this condition.

Had we obtained a positive blood-culture, our diagnosis would have been made. It was not until embolism developed that we actually understood the existing pathologic condition. We could then infer that there must be some endocardiac lesion, which undoubtedly was secondary to a blood-stream infection. The presence of cocci, as shown by a microscopic examination of the valvular lesion, would lead us to believe that this patient had had a coccal bacteremia. The source of the infection may have been the tonsils or teeth, for he had suffered with tonsillitis just one month previous to the onset of his final disease, he had many suspicious-looking teeth, and marked pyorrhea alveolaris.

Endocarditis may be classified as: (1) Rheumatic; (2) syphilitic; (3) bacterial—acute and subacute; (4) indeterminate, including (a) “terminal” or “cachectic” types following or complicating tuberculosis, nephritis, leukemia, etc., (b) so-called atypical verrucous endocarditis of Libman.<sup>3</sup>

It will not be amiss to point out some of the determining clinical and pathologic points of differentiation in the various types of acute endocarditis.

Acute rheumatic endocarditis may be characterized clinically by the history of a pre-existing or existing tonsillitis or chorea, by the irregular fever, excessive sweating, joint-pains, secondary anemia with leukocytosis, and almost uniform absence of embolic phenomena. There is usually no enlargement of the spleen. Cardiac murmurs may be detected—most commonly in the mitral area. Fibrinous pericarditis is a usual accompanying feature. The tender cutaneous nodes of Osler may be found. Blood-cultures are almost universally negative. Rheumatic endocarditis tends to become chronic. Pathologically the heart-valves show vegetations which are small, grayish or pinkish, verrucous structures, uniform in size, situated in a row along the line of closure of the valve. Rarely do these vegetations involve the free edge or chordæ tendineæ. Microscopically, these structures show a mass of agglutinated blood-platelets deposited over an area of edematous and actively proliferating subendothelial tissue. The pulmonary valve is rarely affected. Perivascular lesions are found in the myocardium—so-called Aschoff bodies. No Braecht-Waechter\* lesions. No emboli are found in the glomeruli of the kidneys.

Acute bacterial endocarditis exhibits an acute onset, with a stormy course. Fever may be remittent or intermittent in type, and is usually accompanied by chills. Joint-pains and excessive sweating are not characteristic. Spleen may not be enlarged. There is a leukocytosis. Embolism is a very common accompanying feature. Pericarditis rarely is found and, if found, is

\* A Braecht-Waechter lesion is a round-cell interstitial lesion of the myocardium.

purulent in character. Janeway\* lesions supposedly are characteristic. Pathologically the heart-valves may show large or small, rather friable, usually sessile types of vegetations. Cultures taken from these vegetations usually show organisms, including the anhemolytic streptococcus, pneumococcus, staphylococcus, or gonococcus. Blood-cultures are almost uniformly positive. There are no Aschoff bodies or Braecht-Waechter lesions in the myocardium. Emboli are not found in the renal glomeruli.

Subacute bacterial or infectious endocarditis has an insidious onset. Patient has a sallow complexion, and complains of disability and weakness. Fever is remittent or intermittent in type. There is a progressive secondary type of anemia, with a mild leukocytosis. There may be joint-pains and some articular swelling (not so pronounced as in rheumatic endocarditis). Petechiæ on the skin are characteristic. Osler's nodules may be found. Blood-cultures usually show *Streptococcus viridans*. It is frequently found in persons who have had previous attacks of rheumatism, and infection is usually engrafted on chronically diseased valves. Cardiac murmurs are almost constantly found. Splenomegaly is characteristic. Although there are some recoveries, the usual duration of this disease is not more than two or three years. At necropsy one often finds some form of embolism, such as petechiæ of the skin or conjunctivæ, infarctions of the spleen or kidneys, cerebral embolisms, or embolic glomerulonephritis. Vegetations on cardiac valves are large and villous, rather friable, tend to spread to wall of auricle and downward on chordæ tendineæ. Involvement of tricuspid or pulmonary valve is very uncommon. Pericarditis is seldom found. Aschoff bodies in the myocardium are rare. Braecht-Waechter lesions are commonly found. The *S. viridans* can usually be cultured from the injured valves.

Atypical verrucous endocarditis<sup>3</sup> is so called because of the unusual character of the endocardial lesions and their verrucous appearance. Clinically, none of these patients complains of symptoms referable to the heart before onset of the trouble.

\* A Janeway lesion is a small, non-tender, hemorrhagic nodule presenting itself in palms of the hands or soles of the feet.

None gives a history of chorea. This disease runs a subacute course, from four and a half to nine months. Fever is usually irregular. Excessive sweating is not characteristic. Arthritis symptoms are common. There is a moderate anemia. There is a tendency to a leukopenia, so differing from other types of acute endocarditis. Heart does not show much enlargement. Pericarditis may coexist. Spleen is not palpably enlarged. Petechiæ in the skin and conjunctival mucous membrane are often found. There may be erythematous lesions in the face, like acute lupus erythematosus disseminatus. Blood-cultures are uniformly negative, and valvular vegetations are free from micro-organisms. Embolism is often found. At autopsy one usually finds an organizing fibrinous pericarditis. Vegetations are verrucous, but tend to be larger and less uniform in size than those found in rheumatic endocarditis. Unlike those in rheumatic cases, lesions generally extend both above and below closure line of the valve, often involving free edge in places. Tricuspid valve was involved in 4 cases described by Libman, and pulmonary valve in one case—rarely seen in rheumatic endocarditis and very uncommonly in subacute bacterial endocarditis. There are no Aschoff bodies in the myocardium. Embolic glomerular lesions are never found.

The characteristic symptoms of embolism of the extremities are those of ischemia. The main subjective symptoms are severe stabbing pain, sensation of cold and numbness, and disturbance of sensibility. Objectively, one finds a change in the color of the skin, which may be marble-white, blotchy, ashen, or cyanotic. There is a decrease in the temperature of the part. Motility is disturbed. Skin and tendon reflexes are absent, and there is no pulsation in the artery distal to the location of the embolus. The treatment is either surgical or non-surgical. Heat may be applied with the hope of re-establishing collateral circulation, but this treatment is to be considered only when a very small vessel of the extremity is involved, and when there is no evidence pointing to impending gangrene. Pemberton<sup>4</sup> states that up to the present time less than 150 cases of embolectomy have been reported in the literature, and most of these operations

have been reported by Scandinavian surgeons. The large number of failures in this type of operation undoubtedly accounts for the paucity of the reports. Of the number of cases reported in the literature, about 37 per cent. were successful. The first successful embolectomy was performed by Labey in 1911. He removed an embolus from the femoral artery six hours after its appearance. Key, of Stockholm, performed the second successful embolectomy in 1912. Key states that in no case has operation been successful when performed more than twenty-four hours after onset of obstruction. An early diagnosis and immediate surgery is advocated in order to avoid degenerative changes in the intima of the vessel at the site of the embolism.

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## CLINIC OF DR. THOMAS KLEIN

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### AGRANULOCYTIC ANGINA

SINCE Schultz's description of the group of cases which he characterized as agranulocytic angina in 1922, 49 such cases have been collected from the literature. Kastlin, in the *Journal of American Medical Science*, reported 2 cases and summarized the findings in 43 of these cases. Stengel and Edward Rose have found 6 additional cases, making a total of 49 in all.

This disease, while found both in the male and female, is more common in the female. Kastlin found the average age for the female to be forty-six; the male is somewhat younger, twenty-nine. The characteristics of the disease are an acute onset, occurring in the majority of cases in healthy persons. Occasionally, however, it may occur, as in our case, in persons who have been ill for some time with a chronic disease. There is always a gangrenous stomatitis. The blood-picture is one of a marked leukopenia with an absence or marked diminution of the polymorphonuclear leukocytes. The lymphocytes are relatively increased up to 100 per cent. The bone-marrow at autopsy is intensely red, and there is an absence of granulocytic cells. Regional lymph-node enlargement is usually found. At the onset of the disease, chills, fever, malaise, and the symptoms which usually accompany an acute respiratory infection, are found. Coryza, tonsillitis, pharyngitis, etc., are usually associated. In about one-half the cases jaundice is also a factor. The disease is of short duration, lasting from a few days to as many weeks. The mortality is extremely high, yet a few cases with recovery have been reported. When this occurs, the blood-picture rapidly returns to normal. In a few instances this is



followed in a short time by reinfection or relapse, ending in death. Death is usually caused by a massive pneumonia.

The case which I wish to call to your attention today is one of agranulocytic angina.

Mrs. E. V. B., aged sixty-three years, white, housewife, came to us April 7, 1927, complaining of a chronic arthritis. The disease was of three years' duration. All the phalanges, the shoulders, elbows, wrists, and knees, were involved. Walking was extremely difficult on account of pain and stiffness. There was no cough or expectoration, no dyspnea or precordial pain. She was free from nose and throat symptoms, yet stated that she rather frequently had a slight nose bleeding. She had no headaches or vertigo. Her appetite was poor. Nausea, vomiting, gaseous discomfort, and pyrosis were all absent. Bowels were normal without cathartics. Sleep was disturbed on account of pain. She had lost 20 pounds in three years.

The past medical history is composed of measles, mumps, and chicken-pox, as a child. Peritonitis followed birth of a child in 1900. From this, recovery was extremely slow, requiring five years in all before good health was re-established. A hemorrhoidectomy was performed in 1893. A tonsillectomy was performed in 1924, after which the arthritis had improved. Numerous infected teeth had also been removed in the interim. An antrum infection also occurred after the tonsillectomy, necessitating puncturing and washing out.

The family history is unimportant. Husband living and well. One son living and well. Habits were all normal.

Physical examination: Adult, white, female, well developed, but rather poorly nourished. Weight, 134 pounds. Head, normal in size and shape. Hair, mixed gray. Pupils, equal, and react to light and accommodation. No ocular palsies. Ears, negative. Nose, sinuses all clear to transillumination. Mucous membrane on left side of septum markedly congested with slight ulceration. Ears, negative. Teeth, mostly false. No infection around remaining teeth was found. Tonsils, absent. Tonsillar pillars and pharynx, normal. No cervical glandular enlargement. Lungs, moderately emphysematous. Breasts, normal. Heart, normal size and position; good muscle quality; no murmurs or irregularities were noted. The cardiac rate was 96. Abdomen, rather pendulous. Liver, spleen, and kidneys not palpable. Gall-bladder and appendiceal tenderness was also absent. Extremities: marked deformity of hands, with crepitation and limited motion in all the larger joints. All deep reflexes were normal.

Laboratory findings:

Blood-pressure: Systolic, 160; diastolic, 90.

Blood-chemistry, 4/7/27:

Blood-sugar: 111 mg. per 100 c.c. of blood.

Uric acid: 2.7 mg. per 100 c.c. of blood.

Urea nitrogen: 7 mg. per 100 c.c. of blood.

Creatinin: 1 mg. per 100 c.c. of blood.

Blood-Wassermann: Reaction, negative.

Blood-count:

Hemoglobin: 92 per cent.

Red blood-cells: 4,730,000.

White blood-cells: 3900.

Urine:

Color: Amber.

Specific gravity: 1.021.

Reaction: Acid.

Albumin: Negative.

Sugar: Negative.

Microscopic: Occasional white blood-cell with few mucous shreds found.

Prior to coming under our care she had been taking various types of treatment for the arthritis. Electric cabinet baths, followed by massage and passive motion, colonic irrigations, etc., had all been tried. She had also received 43 injections of Coley's mixed toxins with rather severe reaction. While under our care she received 36 intravenous injections of ammonium ortho-iodoxybenzoate. Nausea and vomiting usually followed the administration of this drug, but soon subsided. The arthritis markedly improved. She did not receive any injections of ammonium ortho-iodoxybenzoate after January 1, 1928, three months prior to her death. This point is of importance because the three months' interim is sufficiently long to rule out any possibility of poisoning from the use of the drug.

On March 27, 1928 she contracted what was thought to be an ordinary head cold or coryza, without fever. Four days later, April 1st, she complained of being partially deaf. This was followed that night by pain in both ears, at which time her temperature went up to 101° F. The following morning both ear drums were opened under gas. No frank pus was found, but only serum exuded. The pain was relieved, but the temperature and coryzal symptoms persisted. The following day, April 2d, a well-marked bronchitis developed, and the temperature went up to 103° F. The pharynx and tonsillar pillars were now intensely congested. The cervical and submaxillary lymph-nodes were quite swollen and tender. The patient was extremely ill and very toxic. At this time we could not make out any signs of a definite pneumonia. The liver and spleen were not enlarged and jaundice was absent. The white blood-count at this time was 1100 and 1000 cells per cubic millimeter (M. Wurst), hemoglobin 93 per cent., red blood-cells 4,510,000. A few hours later, April 3, 1928, the gangrenous stomatitis developed, and at the same time marked edema of the arytenoids was noted. Breathing was extremely difficult and preparations were made for a tracheotomy. Eight hours after the above blood-count the white cells had dropped to 400 cells per cubic millimeter (H. Keeler). At midnight April 3d the white cells had dropped still further. The count now was as follows: Hemoglobin, 91 per cent.; red blood-cells, 4,850,000; white blood-cells, 175. The differential count showed large lymphocytes, 15 per cent.; small lymphocytes, 75 per cent.; large mononuclears, 10 per cent. Two hundred cells were counted. No change in size, shape, or staining reaction of the erythrocytes was noted. The blood-culture was sterile. Smears taken from the tonsillar

fossæ showed pneumococci and micrococci, but no Vincent's or Klebs-Löffler bacilli. Cultures from the same area showed the same organisms.

At this time the temperature mounted to 104° F., pulse 120, and respiration 36 per minute. The patient gradually became comatose and died six hours later. The pulmonary findings at the end were those of a very rapid oncoming massive bronchopneumonia. An autopsy was unobtainable.

Summing up, this patient had all the clinical findings of the condition which Shultz called "agranulocytic angina." It is of interest to note that the patient one year prior to the development of this condition had a marked leukopenia (3900 white blood-cells), and it may have had a rôle in its causation. Leukopenia is very common in chronic arthritic patients. The overwhelming effect of the toxins on the bone-marrow is undoubtedly the cause of the absence of the polymorphonuclear neutrophil. In my mind there is a question whether or not this is a distinct entity, and whether or not this condition would not be found more frequently if we studied the moribund more carefully.

## CLINIC OF DR. H. L. BOCKUS

FROM THE GASTRO-INTESTINAL CLINIC OF THE GRADUATE HOSPITAL,  
UNIVERSITY OF PENNSYLVANIA

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### PYLORIC OBSTRUCTION IN THE NEGRO

THE high incidence of dietary indiscretion, alcoholism, gastritis, achlorhydria, cirrhosis, lues, tuberculosis, and cardiovascular and renal disease in the type of negro presenting himself at the city clinic affords an interesting contrast with the frequently neurotic, recently emigrated Caucasian. The former's relative freedom from mucous and spastic colitis and the various gastro-intestinal neuroses has been particularly noted in our clinic at the Graduate Hospital. We have found that unless he is a malingerer, his symptoms must be given a much graver interpretation than those of his white brother with a more delicately balanced nervous system. For this reason we have become particularly alert to discover organic disease with the onset of any major gastro-intestinal complaint.

Long-standing gastric retention associated with extreme enlargement of the stomach is due in the great majority of cases to so-called pyloric stenosis resulting from a juxtapyloric ulcer. An exceptional case of malignancy with a longer history than is usually encountered may produce the same clinical picture. A fairly large clinical experience with the negro has caused me to study with interest every case of so-called pyloric obstruction in that race. The advanced and unusual nature of the pathologic process which seems to be more frequently encountered in the negro is well illustrated by the following cases:

Case I.—A. J., a colored male, twenty-nine years of age, was admitted to the Graduate Hospital, March 8, 1928. Family history negative. He denies venereal infection. Married three years and has two healthy children.

The only past illness was an attack of pleurisy in 1918. The present illness started in December, 1927 with pyrosis, belching and vomiting, attacks of aching pain and soreness in the midabdomen associated with vomiting occurring every two or three days. He was intermittently constipated, and during the periods of constipation vomiting was more frequent. There is a questionable history of the passage of "tarry stools" on several occasions since the onset. No cough, dyspnea, or night-sweats. For several weeks previous to admission emesis followed any attempt to eat, although no definite history of "retention" vomiting could be elicited. He had lost 15 pounds since the onset of the illness.

He appeared emaciated, was dehydrated, and seemed at least forty years of age. Temperature, pulse, and respirations were normal. The habitus was normal, the skin was dry. A generalized and extensive adenopathy involving the submaxillary, anterior, and posterior cervical, inguinal, and axillary nodes was noted. The glands averaged a size comparable to an almond and were quite hard. The pupils were slightly irregular and reacted sluggishly to light. The chest was of the phthisical type, the supra- and intraclavicular spaces being prominent. Signs suggesting a partial fibrosis of the left apex and the whole of the upper right lobe were obtained. Gastric peristalsis was visible, and a succussion splash indicated a dilated stomach containing fluid.

*Laboratory Data.*—Red blood-cells, 3,710,000; white blood-cells, 10,250; hemoglobin, 63 per cent.; lymphocytes, 47 per cent. Urine essentially negative. The Wassermann and Kahn reactions were strongly positive. The blood chemical studies were negative except for evidence of alkalosis. Sugar, 91 mg. per 100 c.c.; creatinin, 1.6 mg.; CO<sub>2</sub> combining power, 76 volumes per cent. (normal 55); urea, 23 mg.; whole blood chlorids, 440 mg. (normal 560). The stool gave a Grade 4 reaction for occult blood. It was alkaline in reaction and exhibited no excess of fat. Parasites were not found. The gastric analysis was unsatisfactory because of vomiting. The fasting residuum contained a large quantity of gross food. Bile present; HCl 45; acidity, 75. Gross blood, negative. Occult blood, +2. The microscopy was negative except for innumerable yeast-cells and food remains. Gastro-intestinal x-ray revealed an enormous stomach which for the most part was inactive, resembling extreme atony, but from time to time showed exaggerated hyperactive peristalsis. There was 90 per cent. retention of the barium meal six hours after ingestion, 75 per cent. retention after twenty-four hours, and 40 per cent. retention in the stomach after forty-eight hours. The duodenal cap could not be filled out normally under the fluoroscope, but did show almost normal filling on several films. In addition to the retention in the stomach after forty-eight hours, barium was seen in the second and third portions of the duodenum, which appeared dilated, and in several coils of ileum. There were several large opacities visible on a level with the fourth and fifth lumbar vertebra which were believed to be calcified mesenteric lymph-nodes. They were identical on each film (Fig. 180).

*Discussion.*—The patient is a young adult negro with obvious obstruction at or near the pylorus, showing laboratory evidence of alkalosis. Etiologically several conditions must be considered. In any patient, particularly

in the male sex, with a comparatively short (few months) progressive history of digestive trouble associated with weight loss, in whom pyloric obstruction is present, malignancy must be eliminated. Gastric malignancy seemed very unlikely to us because of the presence of a hyperacid gastric residuum and the absence of any semblance of a gastric defect by x-ray. Cancer of the duodenum is extremely rare. The commonest cause of pyloric obstruc-



Fig. 180.—Case I. Twenty-four hours after opaque meal. Note upper two-thirds of stomach well filled. There is fairly good filling of cap at this time. The large globular opacity in the right abdomen is barium retention in an enormously dilated duodenum, suggesting obstruction below this point. The mottled opacities in the lower central and lower right abdomen are due to calcified tuberculous lymph-nodes.

tion in the young adult male is duodenal ulcer, but then a history of stomach trouble for years is usually present before obstruction ensues. However, we have found the history of the duration of illness to be most unreliable in the negro. Autopsy repeatedly shows advanced pathology in many of them, which must have been present for years with complaints of comparatively

recent onset. They are the exact antithesis of the emotional, hypersensitive, splachnoptic, city-dwelling, female Caucasian in that respect. The hyperacidity and occult blood in a stomach containing bile and occult blood in the stool might be explained by a duodenal ulcer. Roentgen-ray studies did not definitely support such a diagnosis. There was no niche or defect in the duodenum which could be assumed to be due to ulcer. Moreover, in cases of duodenal ulcer with pyloric obstruction of this extent, the cap is usually so contracted that it cannot be visualized. The pylorus and duodenal bulb are frequently fixed in such cases due to adhesions. In this case free mobility was present. Although duodenal ulcer could not be definitely excluded, its presence could not be determined. What part does the syphilis play? Syphilis of the stomach is comparatively rare and proved syphilis of the duodenum almost unknown. The absence of a gastric defect by x-ray and the presence of ample acidity militate against a diagnosis of gastric syphilis to account for the gastric retention. In view of the generalized enlargement of superficial glands, the possibility of luetic involvement of the mesenteric glands causing pressure on the pylorus and upper small intestine must be taken into account. Lastly, the suggestion of an old tuberculous process in the lungs, together with the visualization of large calcified mesenteric lymph-glands brings up the possibility of tuberculous mesenteric lymphadenitis as the primary etiologic factor. The cause of the gastric retention is not obvious. Malignancy and gastric syphilis seem unlikely. Duodenal ulcer and obstruction caused by mesenteric glands either luetic or tuberculous seem more acceptable.

*Progress.*—With the marked gastric retention surgical intervention seemed essential. This could not be attempted until the chemical evidence of alkalosis was eliminated. We have found this tendency toward alkalosis so frequent in pyloric obstruction that every case of gastric retention has a routine blood-nitrogen, carbon dioxid combining-power and blood-chlorid estimation. Surgery is always postponed until the chemistry is normal. The mortality from operation for pyloric obstruction has been considerably reduced thereby. I should particularly like to emphasize the fact that quite severe alkalosis may be present as shown by blood chemical findings in the absence of symptoms of alkalosis. In alkalosis due to upper intestinal obstruction, the blood-chlorids seem to be decreased earlier and to a greater extent than the  $\text{CO}_2$  is increased. The blood-urea and non-protein nitrogen are considerably elevated. A 10 per cent. solution of glucose in 500 c.c. of salt solution intravenously was ordered on March 9th. It is our practice to continue administration daily until the blood chemistry is normal. Only five such injections were given because of interruption by certain examinations up to March 19th. On that date the urea had risen to 35 mg., but the  $\text{CO}_2$  had returned to normal. At the completion of the studies on March 18th antiluetic therapy was instituted. Bismuth was selected (sodium potassium tartrobismuthate) rather than the arsenicals because of the presence of pyloric obstruction with disturbed blood chemistry, and the uncertainty regarding the tuberculous process in the lung.

On March 18th the patient developed an acute follicular tonsillitis with a temperature of  $101^\circ$  F. and pulse-rate of 110. The following day a pain

developed in the right chest with some dyspnea. He rapidly became weaker and died rather suddenly on March 21st.

*Necropsy.*—The immediate cause of death was probably an acute sero-fibrinous pericarditis. Cultures taken from the pericardium and also from the pleural sac where a bilateral acute serofibrinous pleuritis was present yielded a pure culture of *Streptococcus hemolyticus*. It is conceivable that the streptococcus infection originated in the tonsil and as a result of poor resistance a bacteriemia developed with secondary involvement of the pleura and pericardium. We are more concerned with the primary cause of the illness. The focus of pathology which caused the clinical picture presented was searched for in the abdomen around the pylorus and the following conditions found:

1. A large chronic ulcer involving the anterior and lateral aspect of the first part of the duodenum. The base of the ulcer consisted of fibrous tissue. No duodenal tissue could be recognized. Chronic peritoneal adhesions existed between the gall-bladder and the duodenum and pylorus. A marked thickening of the peritoneal coat of the gall-bladder was noted. The stomach was enormously dilated, but the pylorus did not appear to be sufficiently closed to account for the degree of retention.

2. A generalized tuberculous lymphadenitis involving the mesenteric glands was present. Several large glands the size of limes were situated around the pylorus and head of the pancreas and undoubtedly were making pressure upon the pylorus and duodenum. A large scar of the spleen was thought by the pathologist, Dr. Case, to be a healed tubercle or infarct. Evidence of a healed tuberculous process of the right upper lobe and adhesive pleuritis of the left apex was found.

*Summary.*—The points of interest are:

1. The exodus of the patient with a streptococcus bacteriemia before the alkalosis could be controlled. We suspect that the presence of alkalosis definitely lowers the resistance against bacterial invasion of the blood-stream.

2. The alkalosis was typical of the type so frequently seen in pyloric obstruction. The history of persistent vomiting suggests depletion of chlorids as the primary factor in the alkalosis. It should be recalled that alkalosis may occur in pyloric obstruction in the absence of vomiting.

3. The primary disease in this instance was undoubtedly tuberculosis, primary in the lung and secondarily glandular. The history of pleurisy, signs of a healed tuberculous process in the lungs, enormous calcified abdominal glands visible by x-ray, and the lymphocytosis in a negro were sufficient to direct attention toward the possibility of *tabes mesenterica*.



4. The history of tarry stools and the hyperacidity were probably dependent upon the presence of duodenal ulcer. It is doubtful if this lesion was the principal cause of the gastric retention. The cap in this instance was more capable of expansion than is usually the case in a duodenal ulcer causing obstruction. The delay in the second and third portions of the duodenum was undoubtedly dependent upon pressure from enlarged glands and it is likely that the gastric retention was in large part due to the same pathology. Attention is directed to the absence of a typical duodenal ulcer syndrome of hunger-pain, periodicity, etc. Duodenal ulcer in the negro is often just as atypical clinically as it was in this case.

Case II.—J. H., a colored laundryman, age thirty-five years, was admitted 1/20/27, complaining of stomach trouble for past four or five years. During this time attacks of epigastric pain occurred two or three hours after



Fig. 181.—Case II. Enormous dilatation of stomach and filling defect on greater curvature resembling outside pressure. Pylorus and duodenal cap could not be seen.

meals about once a month, not relieved by food or soda. Duration of attacks about one day. The attacks were accompanied by vomiting for one year previous to admission, which relieved the pain. For the past three weeks previous to admission the symptoms were much more severe and vomiting was incessant. A hard nodular mass was felt in the left upper abdomen extending from the left costal margin to the level of the umbilicus, descending markedly with inspiration. Gastric analysis: high normal acidity with marked biliary regurgitation. Occult blood negative. Stool: positive for occult blood. Blood-chemistry: sugar, 70 mg. per 100 c.c.;  $\text{CO}_2$ , 68 vol. per cent.; urea, 18 mg. per 100 c.c. Red blood-cells, 3,950,000. Hemoglobin, 65 per



Fig. 182.—Case II. Twenty-four-hour retention in stomach with persistent filling defect on greater curvature.

cent. White blood-cells, 8000; polymorphonuclears, 69; small lymphocytes, 28; large lymphocytes, 2; transitionals 1. On January 25th intractable vomiting and abdominal pain persist. Blood-chemistry reveals an alkalosis.  $\text{CO}_2$  80 vol. per cent.; blood-chlorids 400 mg. per 100 c.c.; van den Bergh, 0.8 unit. Glucose and saline was administered by bowel and vein, which controlled the vomiting. x-Ray (Fig. 181) revealed an enormous dilatation of the stomach without any visualization of the duodenum. A large smooth indentation was present on the greater curvature of the stomach which resembled that due to outside pressure. This portion of the stomach was not fixed. Marked gastric retention was seen at twenty-four hours (Fig. 182). Bromsulphalein liver

function test was normal. Icterus index, 2 units; urobilinogen, normal. On February 2d the hospital record has the following entry: "Summary of significant data includes: (1) History of five years' duration; (2) hard mass in upper left epigastrium descending with inspiration; (3) hyperacidity without bleeding; (4) pyloric obstruction without pyloric irregularity; (5) pressure defect midportion of greater curvature probably due to the palpable mass; (6) tendency toward alkalosis; (7) positive Wassermann. The following conditions must be considered: (a) Obstruction at or near the pylorus associated with a high normal acid curve and long history pointing toward duodenal ulcer; (b) the left lobe of the liver is the most likely site of the mass which may be either luetic or malignant, and is pressing on but is not attached to the stomach." Although the case was obviously surgical from the standpoint of pyloric obstruction we decided to try antiluetic measures, feeling that if the mass were malignant it was certainly inoperable. Sodium iodid, 15 grains, was ordered on alternate days intravenously, together with mercurial inunctions. Blood-chemistry at this time: Urea, 23 mg. per 100 c.c.; CO<sub>2</sub>, 58 vol.; blood-chlorids, 440 mg.; creatinin, 1.6 mg. per 100 c.c. A rise in temperature and pulse-rate occurred on February 6th—pulse-rate 110, temperature 103° F. On the 9th the abdomen was somewhat distended, but free from marked tenderness or rigidity. We were greatly surprised upon feeling the abdomen to note that the mass was not palpable, although it was distinctly felt the preceding day. This inability to palpate the tumor may have been due to distention of the abdomen, but a number of other possibilities had to be considered. The administration of iodids, intravenously, which had been started seven days previously, the fever and the apparent disappearance of the mass caused us to think of the rupture of an abscess, cyst, or a rare parasitic involvement of the liver, like echinococcus or actinomycosis. A number of consultants were of the opinion that a luetic tumor could not possibly recede so quickly on iodid therapy. Coincidentally with the above phenomena the muscles of the extremities became extremely painful and tender, particularly the calf muscles. White blood-cells, 5500. Polymorphonuclears, 78 per cent. A blood-culture had been taken several days previously and on the 9th a hemolytic streptococcus bacteremia was reported. The patient died before serum therapy could be given. Autopsy findings: When the abdomen was opened, to our surprise the left lobe of the liver was found to be extremely small, only a rudimentary lobe being present. The mass which we had felt in the upper left abdomen, about the size of a half orange, involved the jejunum, a loop of ileum and transverse colon. Before dissection it appeared as though a spontaneous anastomosis had occurred between the jejunum and the transverse colon, but this did not prove to be the case. The mesenteric lymph-nodes which were a part of the mass were enormously enlarged, two of them reaching a diameter of 5 cm. A section of these glands showed the center to be of firm consistency having a homogeneous yellowish-white color. Upon opening the stomach and small intestine no evidence of disease was found in the stomach or upper duodenum which could account for the apparent pyloric obstruction. Just below the duodenojejunal junction the wall of the jejunum was thickened to about three times its normal breadth and extensive fibrosis of the intestine and mesentery was present. For an area about 3

cm. in width the mucosa of this part of the jejunum was covered with numerous shallow ulcerations, varying in diameter from 1 mm. to 1 cm. and giving the jejunum a moth-eaten appearance. Several inches below a similar ulcerated area was found. This condition resembled very much that seen in acute suppurative gastritis. The abdomen was free from fluid and there was no evidence of peritonitis. The microscopic examination of the jejunum reported by Dr. Eugene Case shows multiple chronic ulcerations of the mucosa extending into the muscularis. The wall of the intestine is much thickened and there is a dense infiltration of large mononuclear wandering cells, many

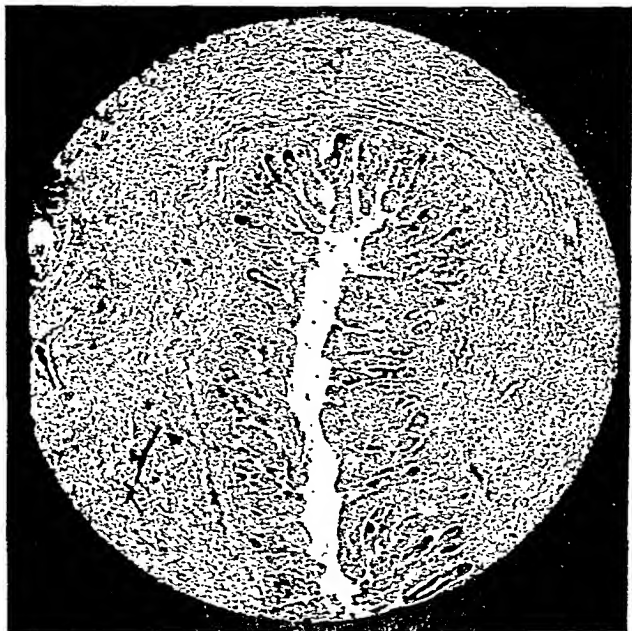


Fig. 183.—Case II. Section from jejunum showing partial destruction of the mucosa. Dense infiltration of mucosa, submucosa, and muscularis with lymphocytes and large mononuclear wandering cells.

of which are phagocytes, lymphocytes, and plasma cells (Fig. 183). Lymph-nodes of the mesentery show a similar type of infiltration (Fig. 184). There is no resemblance to tuberculosis. Lymph-nodes were described as possibly gummatous and the process on the jejunum possibly syphilitic. Space does not permit of detailed discussion, but one might advance the theory that a chronic luetic involvement of the jejunum was the basic lesion with a superimposed subacute streptococcic infection which might have been lighted up by the intravenous administration of the iodid. The necropsy revealed no other focus for the hemolytic streptococcus infection. The inability to find

the Treponema by the Levaditi method makes it impossible to present this case as one of jejunal syphilis.

These 2 cases interested me because they illustrate rarer causes of obstruction near the pylorus easily mistaken for pyloric obstruction. They emphasize certain peculiarities in the negro which one must always consider seriously:

1. Tuberculosis and lues, although rare, will be found a more frequent cause of pathology in the upper gastro-intestinal tract

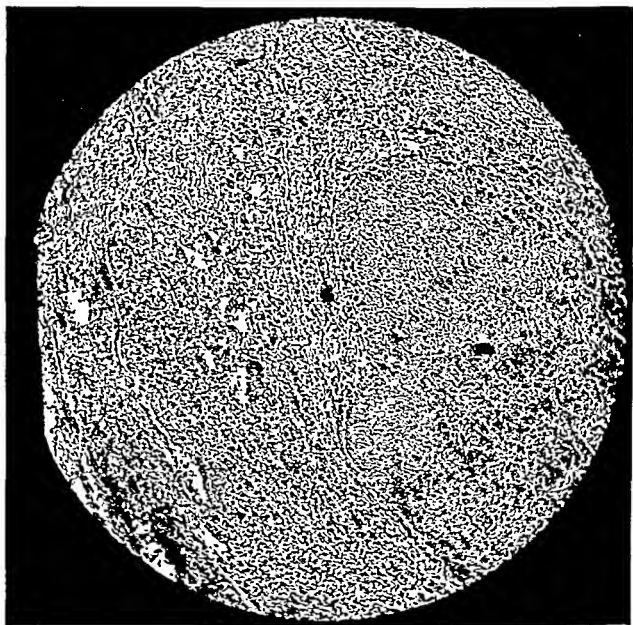


Fig. 184.—Case II. Section from lymph-gland. Capsule thickened. Architecture of gland altered. Cellular infiltration similar to that seen in the jejunum.

2. The symptoms of lesions like peptic ulcer are always much less classical.

3. The amount of pathology found at operation and autopsy has frequently exceeded our preoperative estimate.

Certain lessons which these 2 cases and other not dissimilar ones have taught us are:

(a) The necessity for ruling out alkalosis in every case of suspected obstruction at or near the pylorus. An effort must be made to overcome the alkalosis before any other treatment is undertaken. Detailed studies to determine the cause of the obstruction had better be postponed until the blood has been brought to normal if they interfere with the treatment of alkalosis. Antiluetic treatment would seem to be contraindicated until the alkalosis has been corrected.

(b) We prefer bismuth to arsphenamin in the treatment of leutics with pyloric obstruction. Two of our colored patients with obstruction died during courses of arsphenamin therapy, one from perforation of a duodenal ulcer and a second from peritonitis of unknown origin.

(c) Operation for the alleviation of obstruction, as soon as alkalosis can be eliminated, without further delay seems important. The demise of both cases with a streptococcic bacteriemia is of interest. Antiluetic treatment was being carried out in both. The alkalosis was not entirely relieved in either. Dehydration and alteration of the acid base equilibrium evidently were instrumental in lowering the resistance against infection.

In the first case the portal of entry of the infection was probably through the tonsils. In the second the organisms may have gained access to the general circulation through the jejunum. A chronic, luetic jejunitis may have been converted into an acute ulcerative process by the administration of iodids intravenously.



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SOLITARY ABSCESS OF THE LIVER

DR. BARTLE: Hepatic abscess, like ectopic pregnancy, must ever be kept in mind when the patient presents symptoms which are not clear cut and characteristic of some one pathologic condition. But, unlike extra-uterine pregnancy, in which the diagnosis forces itself upon the surgeon in an exploratory laparotomy, the diagnosis of liver abscess is not made easy by incision and inspection. If unsuspected, there is little possibility of the surgeon stumbling upon the diagnosis as a result of exploratory operation. Indeed, in both the acute and chronic types of liver abscess, the internist, rather than the surgeon, is the more likely to be called upon to make the diagnosis; for in the one septic pneumonia is first thought of, and in the other (chronic) many lung and other liver conditions are simulated. And so this subject becomes an important one to the general practitioner in zones where tropical liver abscess is not prevalent, because he is apt to encounter it and overlook it before the patient comes to either internist or surgeon. For this reason, even though the incidence is still quite low in the temperate zone, we have thought it might be interesting and instructive to present this subject to the reader and, as well, to report one more case in which the etiology is still unknown.

In the tropics the incidence of abscess of the liver is fairly high; one writer—Ludlow<sup>1</sup>—in 1926 reported 160 personally observed cases. All of Ludlow's cases were thought to have resulted from amebic dysentery of long standing, which either



had been incompletely treated with emetin, or else had had no emetin at all. Many cases of amebic ulceration of the large bowel (presumably *Entameba histolytica* infestations) in the white race had been properly treated without one liver abscess developing. Abscesses were confined to the natives—Koreans—and apparently resulted only after prolonged infestation. Other students of tropical hepatic abscess reverse these figures, reporting many more cases among the non-native population of Siam, China, and India than in the native population. Ludlow, in quoting Bressot, asserts that prior to the Great War amebic hepatitis (liver abscess) was unknown in France; but now cases are being reported elsewhere than from the tropics.

He believes, with Sobell and Rogers, that all tropical liver abscesses, whether single or multiple, are not true abscesses, but result from a primary hepatitis. The *Entamebæ histolyticæ*, carried from the submucosal abscess pocket in the wall of the colon by way of the inferior mesenteric and portal veins, form a thrombus in the terminal radicles of the portal vein, escape into the liver tissue, bring about necrosis by proteolysis—at times amounting to almost complete destruction of the liver substance—and build up a connective-tissue wall in which they live, inclosing the area of liquefaction. Liver abscess has not resulted after bacillary dysentery. In most instances the pus is sterile, but there have been found at times *Staphylococcus albus* and *S. aureus*, *Bacillus coli*, and *Pneumococcus*. In 90 per cent. of Ludlow's 160 cases there was a solitary abscess; and the size of the single abscess varied from a volume of 30 c.c. to as much as 3 liters. The pus was either a thin grape-juice-like fluid or a thick chocolate material which had to be scooped away. Almost all abscesses developed slowly; the average time of illness was thirteen weeks, but some cases had been ill as long as forty weeks. Seventy-four per cent. of these abscesses were in persons between the ages of twenty and fifty years, the males showing eight times the incidence of the females.

According to Abt<sup>2</sup> solitary abscess is extremely rare in children, even after entamebic dysentery (Ludlow had 3 cases before the age of ten years, and 5 cases between eleven and twenty

years). A single abscess in childhood is usually due to infection and suppuration of a hydatid cyst, infection ascending along the biliary ducts from the duodenum, or else through the plugging of the ducts by ascarides which have passed through the ampulla of Vater.

Eliason, in 1926,<sup>3</sup> reported 12 personally observed cases of hepatic abscess following appendectomy, and of these 7 were solitary and were found in the right lobe. Culture of the material showed as the infecting organism: *Streptococcus*, 4 cases; *Staphylococcus*, 3 cases; *Bacillus mucosus*, 1 case; *B. coli*, 1 case; and the culture was sterile in one case. In none of these cases could a history of a precedent dysentery be obtained. Nor was Cort<sup>4</sup> able to obtain a definite history of a previous attack of dysentery in 18.5 per cent. of his 97 cases of amebiasis of the liver. Rogers, quoted by Simon<sup>5</sup> in his excellent monograph on entamebic dysentery, failed to obtain such a history in 19 out of 63 fatal cases of abscess. On the other hand, in known cases of amebic dysentery, liver abscess was found in 20 per cent. by Rogers, 25 per cent. by McDill, 23 per cent. by Strong and Musgrove, and 33 per cent. of fatal cases of dysentery by Craig.

It seems that carriers of dysentery are rather more prevalent than we had suspected—similar to the carriers of diphtheria. In two recent and very instructive studies of intestinal protozoiasis, Smithies<sup>6</sup> found more than 7 per cent. of nearly 4000 cases, in which stools were carefully studied, harbored protozoa of various types—*Entameba histolytica* 1 per cent.; and he quotes Craig<sup>7</sup> who states "that approximately 10 per cent. of the inhabitants of the United States harbor *E. histolytica*, while only relatively few of these carriers develop so-called amebic dysentery."

These are very striking figures, and necessarily one pauses to wonder if amebiasis may not be increasing rapidly in the temperate zone; and if so, may we not soon see more abscesses of the liver, spleen, lung, brain, genito-urinary organs, bones, and skin—due to this protozoön—than we have observed previously?

Yet the controversy is still being carried on as to when an ameba is histolytica and when it is not. Paulson and Andrews<sup>8</sup> working at the Johns Hopkins Hospital studied the feces of 253 persons of all types applying at their clinic, and found not one case infested with *Entameba histolytica*, although more than 17 per cent. of these cases showed *E. coli*—a non-pathogenic commensal protozoön. Other students of the entameba believe that it is difficult to identify surely the *E. histolytica*. Stitt<sup>9</sup> says: "Wenyon and others have recently emphasized the difficulties of differentiating human ameba in the vegetative stage, and consider the criterion of presence of red cells in the ameba as the sole valid one indicating the pathogenic ameba. With a dysenteric stool containing ameba but no phagocytized red cells the probability is that it is a stool of bacillary dysentery. The reliable method of differentiating ameba is examination of the cysts, and as these alone are of practical importance in infection, only such forms need be considered in carrier examinations; . . . the chief factor in the spread of amebic dysentery would seem to be the encysted ameba in the stools of the convalescents or healthy carriers rather than the motile ones in dysenteric stools. Our present view is that the carrier is the chief factor in the spread of amebic dysentery, and when such an individual has to do with the preparation of food he becomes a particular source of danger."

We have, then, as has been pointed out by the foregoing dissertation, various direct causes of abscess of the liver—the outstanding one, according to the available literature, is thrombosis of the intrahepatic portal vein by *Entameba histolytica*. Among the other exciting causes should be added focal infections in gastric or duodenal ulceration, and in the appendix, in the gall-bladder, the pelvic organs, and anal region. It must not be forgotten, as pointed out by the Fergusons,<sup>10</sup> that hepatic abscess may result from infection entering the liver by way of a puncture wound as well as by extension from neighboring organs through the lymphatic and arterial streams. Predisposing causes seem to play an important part as well—lowered resistance through

previous malarial infestation or typhoid infection, unusual dietary or alcoholic indiscretions, unaccustomed exposure, and postoperative asthenia.

The onset of symptoms in a pyemic process is very rapid—only a few days sufficing to make a diagnosis possible—but in the amebic or so-called tropical abscess, weeks and months may pass by before the symptoms and signs have become characteristic of this lesion. The formation of the abscess cavity with its hard cicatricial wall is essentially a slow process.

The general symptoms may be listed thus: Chills or chilliness, sweats without regular periodicity, saw-tooth temperature curve, malaise and jaundice (in about 16 per cent., and then only when the abscess is extensive enough to make pressure on the biliary ducts). The patient appears ill, with nervous system impaired, and he may not be able to recite any symptoms pointing particularly toward the liver as the seat of his trouble, perhaps because of a peculiar hebetude which is frequently associated. Leukocytosis is usually present without a disproportionate increase of the polymorphonuclear cells (rarely more than 70 per cent.) and with possibly more than the normal 1 to 3 per cent. of eosinophilic cells; so that the blood-count is not characteristically helpful except for the relatively low polymorphonuclear cell-count, or a possible eosinophilia of from 3 to 10 per cent. is found.

Locally: There may be pain or vague soreness within the liver area referred to the right shoulder or scapular region, and usually intensified by the motion of rotation or bending, but not necessarily by jolting, such as heel-dropping. There may be edema of the tissues over the lower right costal cage (particularly in the acute fulminating abscess) and tenderness of the skin in this area. Deep percussion or finger-tip concussion in the intercostal spaces, as pointed out by Eliason<sup>3</sup> and others, will invariably elicit deep-seated tenderness—a valuable sign. Moderate rigidity of the right rectus muscle is usually present. This is far from a helpful finding, for various observers have encountered either extreme rigidity or none at all in the same types of abscesses. Ascites is rarely present. Careful percussion and

palpation of the liver will always disclose it to be enlarged irregularly. The Roentgen-ray examination lends its greatest help in ruling out suspected pulmonary or pleural involvement, rather than by giving us any positive information about the liver itself, other than as to size of the organ, its shape (particularly of the dome) and limitation of motion with respiration or fixation of the diaphragm. Finally, aspiration of a suspected intrahepatic collection: The needle is inserted in the ninth interspace in the anterior axillary line or at the point of greatest swelling or tenderness to a depth of 3 or possibly 4 inches.<sup>1</sup> Of course only a positive tap is helpful in a diagnostic way. The pus obtained may be thin or thick and viscid, odorless, and resemble cocoa; it is usually sterile and rarely contains amebæ even in a warm stage preparation. When seen the amebæ have recently come from the fibrous wall of the abscess cavity, where by light curettage they can usually be found.<sup>5</sup> Aspiration is a procedure which would seem to be dangerous, yet those physicians who see many of these cases apparently resort to tapping an abscess as confidently as do we in performing pleural paracentesis. Indeed, many cases have been reported in which cure has been effected by repeated "tapping" of the cavity, and without incision. Ludlow<sup>1</sup> thinks so highly of the procedure that apparently he has given up the open operation in which he had a 11.1 per cent. mortality, and has adopted aspiration (repeated as indicated) because by so doing he has reduced his mortality to 2.3 per cent. (one death in 43 aspirated cases) and has shortened the period of hospitalization from an average of twenty-six days for the open operation cases to fourteen days for the aspirated cases.

In the differential diagnosis of hepatic abscess the following conditions must be considered: Empyema, pulmonary abscess, malaria, cholelithiasis, cholecystitis, cholangitis (all three of which are made easily now through Lyon's method<sup>11</sup> of non-surgical biliary drainage), subdiaphragmatic or somatic abscess, liver tumors (cirrhosis, gumma, carcinoma, and hydatid cysts), blood dyscrasias leading to liver enlargement, renal enlargement (pyelitis, pyonephrosis, and hydronephrosis).

The sequel to hepatic abscess without operative interference is death or rupture.<sup>12</sup> The latter occurs in 25 to 28 per cent. of all abscesses into the following regions: Peritoneal, pleural, or pericardial cavity, subdiaphragmatic space, lung, stomach, bowel, kidney, hepatic veins or inferior vena cava, or through the skin in the lumbar region.

### REPORT OF CASE

J. I. B., age thirty-eight years, Irish extraction, journalist, Washington, D. C. He is married, has six children, and has used alcohol rarely—very moderately. He has traveled extensively: West Indies, 1916 to 1917; British Isles, Belgium, France, Switzerland, Italy, Germany, Poland, Russia, Austria, Hungary, Czecho-Slovakia, Jugo-Slavia, and Roumania, 1920, 1921, 1922.

Referred by Dr. Joseph A. Moore and Dr. Thomas J. Fleming, August 30, 1927.

**Chief Complaint.**—Weakness, loss of weight (from 180 to 123 pounds within six months), vomiting, fever for past six months.

**Previous Illness.**—With the exception of a small fistula in ano (1908) and of constipation he had always considered himself well until four years ago, when, in October, 1923 (after one year's residence in Washington, D. C.), he was admitted to St. Joseph's Hospital, Philadelphia, suffering with diarrhea (10 to 30 stools in twenty-four hours), tenesmus, abdominal pain and tenderness, ulceration of the sigmoid, weakness, and loss of weight. Through the courtesy of Dr. Joseph A. Moore, who made the laboratory examinations at that time, I am able to quote the following:

**Urine** (Three Specimens).—Nothing significant.

**Feces.**—Occult blood, negative; no ova or parasites; few red cells; Gram stain—equal number of Gram-positive and Gram-negative organisms.

**Blood.**—Hemoglobin, 82 per cent.; erythrocytes, 4,560,000; leukocytes, 11,800; differential: polymorphonuclears, 68 per cent.; lymphocytes, 19 per cent.; mononuclears, 13 per cent.; eosinophils, 0. Wassermann negative.

**Ulcers in Sigmoid.**—Smears and cultures showed a Gram-positive diplococcus, somewhat lancet-shaped, resembling the organism described by Bagen. Vaccine made from this appeared to cure the condition.

Within six weeks after starting the administration of the autogenous vaccine the diarrhea had stopped, but during those three and a half months the patient had lost in weight 100 pounds (from 196 to 96 pounds). For the next two years he was well and regained most of the lost weight.

One year ago he had a saw tooth temperature (as high as 103° F.) for ten days, without any other symptom.

**Present Illness.**—In April, 1927 he again ran a hectic type of temperature (99° to 102° F. in the late afternoon) which continued, without other symptoms, for three weeks, when hiccough started and continued for five days; and this was followed by continual vomiting for three weeks. Since then fever (100° to 103° F.) and vomiting have been present irregularly. It was not until August 1, 1927 that diarrhea began again, lasted for one week, and

ceased promptly after one non-surgical biliary drainage. On August 15th he began to have sharp lancinating pains in his right shoulder (acromion) on movement, referred down the right chest to the right hypochondrium, intensified by deep breathing, and without cough or expectoration. Along the right costal margin there was a feeling of soreness as of a muscle bruise. For the three days preceding my examination there had been rectal tenesmus and mushy bowel movements. Temperature rarely had been above 99° F. in the afternoon. There had been loss of weight (47 pounds in six months); nervousness and disturbed sleep, for which allonal had given unsatisfactory relief. There had been some weakness, but the trip of 100 miles to Philadelphia by train had not produced a prostrating fatigue.

**Physical Examination.**—August 30, 1927. Weight, 123 pounds. He showed evidence in the shallow, wrinkled skin of great loss of weight. Jaundice was not present in the bulbar conjunctivæ. He was evidently unusually alert when in health—the dynamic mental type—but, on questioning, was extremely nervous, yet sure of his facts.

The head, mouth, and tonsils were negative except for some recent stumps resulting from the extraction of teeth which probably had had apical infection.

The chest was negative for aneurysm, for pleural effusion, for active tuberculosis or new growth of the lungs, but there was hyperesthesia of the skin present over the whole right side. The heart area was normal, and the sounds were pure but rather weak; rate 100 with blood-pressure readings—systolic, 110 mm. of mercury, and diastolic, 75 mm.

The abdomen on inspection and palpation presented a mass in the right midepigastrium. It was slightly tender, smooth and hard, suggesting a tense distended gall-bladder, and apparently continuous with the right lobe of the liver. The lower edge of the liver was sharp, moderately tender on jolting percussion, and easily felt three fingerbreadths below the costal margin in the right anterior axillary line. The spleen was not enlarged; the appendix was not tender; there was no edema of the skin over the liver area, nor was there spasm or increased resistance of the abdominal muscles.

The extremities were negative.

**Rectosigmoidoscopic Examination.**—The anus was normal in tone, and negative for scars, induration, fissure, or hemorrhoids. The prostate was of normal size and without induration or tenderness. The 8-inch sigmoidoscope revealed in the rectum and sigmoid six or eight small linear superficial ulcerations from  $\frac{1}{4}$  to  $\frac{3}{8}$  inch long, covered with a white mucoid film, bleeding readily, but without induration or overhanging margin. Houston's valves were not involved in the ulcerative process. Smears and cultures of the exudate from these ulcers were made, about which Dr. Moore reported as follows:

Sigmoid ulcers: Diplococcus of Bagen.

Stools: Occult blood positive.

No ovæ or parasites (warm stage).

Red cells present.

Leukocytes present.

Urine negative: Large amount of indican.

Blood: Kahn negative.

Icterus index, 7.

Non-protein nitrogen, 30 mg.

Hemoglobin, 77 per cent. Red blood-cells, 5,140,000; white blood-cells, 13,300; polymorphonuclears, 66 per cent.; lymphocytes, 25 per cent.; mononuclears, 6 per cent.; eosinophils, 3 per cent.

No plasmodia malarie.

*Biliary Drainage* (Non-surgical, Lyon's Method).—Magnesium sulphate stimulation produced a prompt return of 120 c.c. of very dark brown (almost black) bile. Microscopic examination of the few mucous flakes obtained in this large quantity of static bile showed a few white blood-cells; no gall-bladder or duct cells, and no crystals.

Culture was sterile.

Following the diagnostic drainage of the gall-bladder the mass in the gall-bladder region was less easily felt, although still present.

*Subsequent Course*.—Four other biliary drainages were as negative of findings as was the first, and all cultures of the bile were sterile, which definitely ruled out the gall-bladder as a source of his trouble. An autogenous vaccine prepared from the streptococcus of Bergen was administered for the subsequent three weeks, during which time biliary drainage was practised at weekly intervals, and salol and bismuth were given by mouth. The stools ceased to be mushy at once, the liver was reduced in size, receding beneath the costal margin, but a mass was still palpable in the right midepigastrium. The patient felt better, was stronger, ceased losing weight, and even gained 3 pounds. On September 23d he had a profuse night-sweat, followed by a profound chill, together with an increase of pain in the whole of the right chest, so that breathing and a recently developed cough caused great suffering. To lie on the right side was impossible, and any motion of the trunk caused all his symptoms to be more pronounced. There was definite finger-point intercostal tenderness in the eighth and ninth interspaces in the posterior axillary line. Physical examination of the chest was negative, and the fluoroscopic examination by Dr. John T. Farrell, Jr., showed there was no gross evidence of disease change in the lungs. The diaphragmatic excursion was free and equal on the two sides, without evidence of limitation of motion. The dome of the liver was smooth with no suggestion of abscess on its superior surface. The bowel movements were normal. The mucosa of the rectum and sigmoid was dry, and all evidence of ulceration had vanished.

By letter Dr. J. Arnold Bergen stated that he had never seen hepatic abscess follow a streptococcic infection of the colon from which the organism bearing his name had been recovered. However, a diagnosis of liver abscess was definitely made, especially since repeated biliary drainage had so conclusively shown the gall-bladder and the freshly secreted bile to be normal. With the concurrence of his family physician, Dr. Fleming (who, it should be known, from the first had suspected abscess), and of the pathologist, Dr. Moore, surgical interference was decided upon, and the surgeon called in.\*

\* Report from Mr. B. on July 30, 1928. "Never better; eat normally; weight 165 pounds; work like a horse. I really cannot tell you how completely I have recovered. I feel fine. Since April 1st I have been working very hard at a very difficult task. I put in long hours, in the most chaotic atmosphere, but I seem to thrive on it."



DR. ELIASON: Surgical Aspect.—Abscess of the liver is a surgical condition, and when single, as in this patient, it should be cured by surgical means. Solitary abscess occurs usually in the right lobe for obvious reasons, chief of which is the fact that the site of the infection is usually in that portion of the portal system that drains into the right lobe. Furthermore, for some obscure reason these abscesses appear to extend peripherally and upward with a tendency to rupture beneath the diaphragm, causing a subdiaphragmatic abscess. The fact that the tendency to point is upward is reason enough for so directing the surgical attack. Intercostal tenderness, superficial edema of the lateral chest wall, lung and pleural reactions, together with fluoroscopic evidence of a high diaphragm with limitation of motion would indicate abscess in such position. Occasionally the abscess occurs on the under surface of the liver, usually near the anterior border of the organ. Local tenderness, enlargement with upper quadrant rigidity, is suggestive, as was the case with this patient.

The above findings should indicate the type of surgical approach and did so in this case, but with some confusion. Because of an enlarged, tender Riedel's lobe, an abdominal approach was undertaken.

*Operation.*—Through an upper right paramedian incision the abdomen was opened, exposing an enlarged liver, the inferior half of which was so soft that it could be folded back upon itself. In the lateral aspect of the dome of the liver there was an extremely hard globular mass approximately the size of a grapefruit. There were no areas of fluctuation and no evidence of adhesions on the liver surface. An exploring needle was inserted into this mass which was placed well up under the costal border. The needle met with almost cartilaginous resistance as it passed through what proved to be the abscess wall. The pus was located at a depth of 2 inches from the liver surface. Ten c.c. of pus was withdrawn and 10 c.c. of lipiodol was injected into the cavity as the needle was withdrawn. A drain was carried up to the puncture in the liver. With one hand in the abdomen and one hand against the chest wall, it was found that the abscess presented laterally about opposite the eighth rib in the midaxillary line. The abdominal wound was closed and through a lateral incision a portion of the eighth rib, 3 inches long, was removed subperiosteally. (When the abscess cannot be located by a hand within the belly, as in this case, it is reached with the aspirating needle, more or less blindly via the chest wall and diaphragm except that the intercostal tenderness to finger-tip percussion is a good guide. When the needle finds the pus, leave it *in situ* until the rib is removed, then after indicating its depth on the needle shaft, it is withdrawn, after first pushing the pus out of its lumen by sterile water, thus minimizing the possibility of dragging a drop of pus into the pleura before adhesions have occurred.) A Michel clamp was attached at each end of the wound and the wound then packed with gauze. This is the first stage of the transthoracic approach—the one of choice for these cases. An x-ray was made the next day and the lipiodol in the abscess was shown to be just inside and at a depth of 2 inches from the rib resection as shown by the Michel clamps (Fig. 185).

*Second Stage.*—Two days later, under local anesthesia, the pleural layers were sutured to the diaphragm, although adhesions appeared to have occurred

obliterating the complemental space. With the electrocautery a puncture wound was made through the pleura and diaphragm into the liver. It was noted that the liver was not adherent to the diaphragm, so the abscess was not opened, but a gauze strip was packed around the liver opening and the third step of the operation postponed for two days. The operation is usually completed in two stages, but absence of adhesions between the liver and the diaphragm rendered it unsafe to liberate pus at this time.

*Third Stage.*—With no anesthesia an aspirating needle was inserted into the cautery scar in the liver. At a depth of more than an inch thick pus was reached. The cautery was then inserted along the needle as a guide. It is

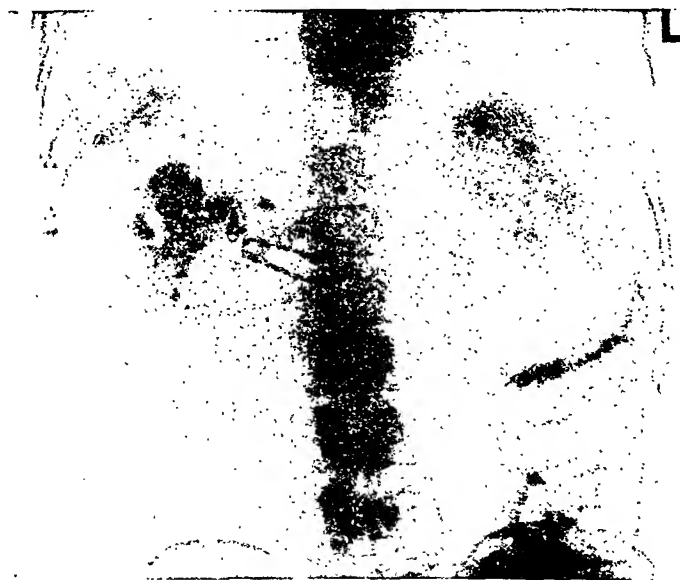


Fig. 185.—Showing the lipiodol in the abscess cavity.

important not to withdraw the needle when it is once in the abscess cavity, as the direction may be lost. The cauterization was stopped at intervals to allow the tissues to be cooled by water, as the patient complained not of burning but of the heat. The track made by the cautery was made as large as desired as it was pushed forward—important, because when once the cautery liberates the pus it is cooled so rapidly that no further enlargement of the track is possible. In this case the opening would permit the insertion of the thumb. After the evacuation of about 600 c.c. of pus the cavity was explored and found to be about 4 inches in diameter. A drainage-tube was sutured in place.

*Postoperative Course.*—The patient made an uneventful recovery and following dakinization the thick, ropy pus soon became thin and rapidly

diminished in quantity, so that the tube was removed three weeks from the time of its insertion. An x-ray of the chest showed no pathology in the lungs or pleuræ; adhesion of the right diaphragm to chest wall as a result of the operation; and no cavity demonstrable in the liver.

*Comments.*—Surgically these cases are best treated through the thoracic route, under local anesthesia, with a two- or three-stage operation, using the cautery guided by the exploring needle.

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## CLINIC OF DR. RICHARD A. KERN

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### SOME CAUSES OF FAILURE IN THE TREATMENT OF BRONCHIAL ASTHMA

PERHAPS the subject had better be worded "a few causes," for the problem of the treatment of bronchial asthma is such a large one that its adequate discussion is beyond the scope of a single clinic. Moreover, we may speak of only a "few" causes of failure, for even at best there are all too many failures, the causes of many of which are probably as yet unknown, while others are beyond remedy, such as the late effects of the disease—emphysema and severe myocardial damage. However, certain causes of failure are repeatedly encountered by those to whom many asthmatics are referred. They are the common causes of failure in treatment at the hands of the referring physician, and to these we will turn our attention.

If a single word were sought to qualify the various causes of failure, the one that would fit most cases is "incomplete"—incomplete diagnosis, incomplete treatment. This cannot be overemphasized. When an asthmatic is referred to the specialist only rarely does he find that the case has been adequately studied by the referring doctor as to causes. This is perhaps not to be wondered at. More to the point is this: When the patient is sent back to the referring doctor with recommendations for treatment, time and again the treatment fails because the recommendations are incompletely carried out. This is not carping criticism, it is simply the statement of what very often happens. The majority of asthmatics are and always will be treated under the direction of general practitioners, therefore, in

a clinic for the practitioner this side of the question deserves special emphasis.

Incomplete diagnosis is due in the first place to an incomplete history. Few know how to take a satisfactory history of an asthmatic's illness. Senior medical students and interns in the clinic who can write a perfect history in an obscure gastrointestinal or nervous disorder turn out a wretched product on their first few attempts in asthma. The practitioner, who is more remote from his didactic training or whose student days antedate the more recent advances in our knowledge of asthma, probably does quite as badly as the student.

Yet a complete history is a *sine qua non* for a complete and correct diagnosis. It is difficult to take such a complete history because to do so presupposes an adequate knowledge of the subject. One must know the various factors that may be concerned in the etiology of the disease. Space does not permit a statement of the known factors in the etiology of bronchial asthma—with these the practitioner should familiarize himself by a study of some recent system article on the subject.

However, certain important points in the clinical history may be mentioned. The story of the beginning of the patient's illness is particularly important. What was the type of the earliest symptoms before later complications (such as infection and emphysema) obscured early causes? Were there clear-cut paroxysms of dyspnea (most likely involving hypersensitiveness) or was the early story one of recurrent "winter colds" or "bronchitis" (infection the important factor) with dyspnea only as a later development? What were the circumstances attending the attacks, especially the earlier ones? Such circumstances are: *Time of day*: House-dust, feathers, horse-hair (mattress) are causes which are more often operative at night. *Season of the year*: Seasonally occurring factors include pollens, some foods, and often infection, as in the asthmatic whose trouble is ushered in twice a year, in the early spring and the late fall, by a respiratory tract infection. *Relation of attack to food* ingested may at times be encountered. *Relation of symptoms to locations*: This is at times very striking when an

underlying cause is a strictly local one, such as the dust of a particular house, the exposure to a sensitizing substance in an occupation, or to animal epidermal proteins: bedding, upholstery, household pets, domestic animals, furs. *The exposure to animal epidermal substances* should be made the subject of direct inquiry—few people know the actual contents of bedding; all patients should submit actual samples for identification by the physician. *Exposure to organic dusts* must be remembered; for example, in the patient's occupation: Grain-dust (farmers, grain-handlers, bakers), wood-dust (woodworkers, jewel polishers), powdered drugs; cosmetics (orris root, rice powder, hair-dyes); freshly dyed fabrics. *Age of onset*: Asthma beginning early in life is usually of allergic origin. *Other manifestations of allergy*: The occurrence of such conditions as hay-fever, infantile eczema, urticaria, food or drug rashes in a patient's history points strongly to an allergic basis for his asthma. *Family history*: The tendency to hypersensitiveness is a strikingly transmissible characteristic, and the presence of a positive family history of allergic disease is a strong argument for believing allergy the underlying factor in a case of asthma.

Incomplete diagnosis may be the result of incomplete examination.

Skin tests must be made with *all* the organic substances to which the patients may be exposed. Multiple sensitization is the rule; therefore, the finding of one or two positive reactions among the first few substances tested does not warrant the termination of testing. House-dust is such a common factor in asthma that it should always be used in testing. Nor are stock samples of house-dust extracts always adequate—house-dusts obviously vary extremely in their composition. A test should, therefore, always be made with an extract of the patient's own house-dust. In the case of furs it is to be remembered that the names current in the modern fur trade are often misleading: Hudson Bay seal is really muskrat; caracul is often goat-hair; rabbit, cat, skunk, and fox may occur in various disguises.

A complete nose and throat examination is essential, yet only too often it is incompletely performed. There should first

be made a careful clinical examination, including transillumination of the sinuses and the use of the nasopharyngoscope. There should then be made an x-ray study of the sinuses. It is essential that both clinical and x-ray examinations be made in every case. Schenck and the writer in an unpublished study of sinus pathology in 200 asthmatics have found that neither examination is in itself adequate. The clinical examination is limited in its possibilities: Only antra and frontal sinuses may be transilluminated; evidence of ethmoid and sphenoid disease is indirect; the presence of pus or polyps and other organic obstruction in their drainage areas suggests trouble, but the absence of these findings does not rule out disease of these sinuses. On the other hand, clouding of a sinus in an x-ray plate is evidence of sinus disease, present or past, active disease or the result (thickened lining) of disease long past. Recent acute sinusitis, demonstrable clinically, may fail to give x-ray evidence. Again, antra clear on transillumination but cloudy on x-ray examination have been shown at operation to be diseased (in two instances such an antrum was filled with a gelatinous material teeming with streptococci). Finally, not the least source of error is incompetence on the part of the rhinologist or the roentgenologist.

**Incomplete Treatment.**—The failure to meet all treatment indications in a given case is a common cause of failure of treatment. If only two of three possible causes are taken care of, the remaining factor may be quite sufficient to continue the trouble. Yet the tendency is only too often to remove one obvious factor, then “wait awhile for results.”

Not only must all indications be met, but each factor must be completely handled. So, for example, in the case of foods, the patient should avoid if possible all reacting foods, including those which reacted only questionably as well as those which reacted strongly. If the patient from experience suspects a certain food, it should be avoided even though it reacted negatively. In the case of hypersensitiveness to inhaled substances the attending physician must make sure the patient really avoids contact. For instance, the asthmatic sensitive to feathers is not relieved by a change to a cotton pillow, because his room-

mate continues to use feathers or because of the presence of feather pillows in a connecting room. Getting rid of the feather pillows may not suffice, the mattress on which feather pillows have lain for years is permeated with feather dust and must be replaced by a new one. Giving away the family cat does not remove all traces of cat-hair and dandruff from the living-room furniture; that requires a thorough cleaning.

Attempts to render the patient less sensitive to unavoidable substances should always be made. The commonest examples are the pollen cases. Treatment with house-dust extracts and various hair and feather extracts has also proved efficacious. A relative tolerance for unavoidable foods (eggs, milk) may be established by the regular feeding of minimal, then gradually increasing, amounts of the food in question. For details of therapeutic technic the reader should consult the literature on the subject.

The complete eradication of nasal pathology is particularly important. This does not mean the resection of every crooked septum, but it does mean the alleviation of contact points between septum and turbinates, the removal of polyps, and the adequate drainage of all suspicious sinuses, sinuses which clinically or by x-ray show any evidence of pathologic change. It is often difficult to convince the rhinologist that sinuses clinically negative but pathologic by x-ray must be opened (unless the rhinologist has had sufficient experience with asthmatics). He will cheerfully wash out a suspected antrum, but may hesitate to drain ethmoid and sphenoid sinuses; yet these sinuses are most often the source of trouble.

In the presence of sinus infection surgical drainage should be supplemented by the preparation and use of an autogenous vaccine. A sputum vaccine should be used if there is bronchial infection.

In addition to specific treatment, certain adjuvant measures should be kept in mind. Allergic individuals more or less readily become sensitized to additional substances with which they may come in contact if that contact is sufficiently intimate and prolonged. It is well, therefore, to advise patients, irrespective



of skin reactions, to avoid feather pillows and horse-hair mattresses, using cotton or kapok (provided these react negatively). They should not have animal pets. Their bedrooms should be as free as possible of dust catchers or dust producers; no rugs, therefore, and no upholstered furniture, but a bare floor (or linoleum). Fiber-rugs and mattings should be banned from the whole house. Asthmatics should eat their chief meal at noon, then only a light supper, and nothing at night. Especially are cold foods (ice cream) to be shunned at night. Marked changes of temperature are to be avoided when possible; the asthmatic should not sleep with a wide-open window in winter.

Climate plays a minor rôle in the etiology of asthma. A change of climate, therefore, is not often likely to effect a cure of asthma. Climatic change may be efficacious in one of two ways: The avoidance of some local sensitizing cause (*e. g.*, pollen) and, what is more important, the lessening of chance for respiratory infection. The points to be remembered are: An equable climate is best, one without wide temperature fluctuations; a dry climate is better for those with considerable bronchitis and excessive sputum; a moist climate for those with dry cough and scanty tenacious sputum; altitudes over 1000 feet are undesirable, at or near sea level is best.

Drugs for symptomatic relief are often enough resorted to, but their mode of application is not always the wisest. Adrenalin is too often given in too large amounts and in too great a concentration (1 : 1000) and, therefore, it often gives rise to undesirable side-effects. The severe nervous reaction which some patients experience from too large a dose of adrenalin leads them to fear and shun the drug and at times to seek relief in the use of morphin with resultant habit formation. Small doses (2 to 5 minims) and lower concentrations (1 : 2600, 1 : 3200) should always be tried first. The drug should be given early in the attack—a few minims at the onset may cut short a paroxysm, while 15 or 20 drops may fail to relieve adequately when an attack has lasted for some hours. Small doses can and should be repeated as often as needed. Pituitrin and adrenalin (equal amounts) at times relieve when adrenalin alone fails. Ephedrin

in full doses produces in some patients marked nervousness and severe insomnia that are nearly as disturbing as the asthma itself. In such patients smaller doses,  $\frac{1}{4}$  or  $\frac{3}{8}$  grain, may relieve dyspnea without producing the disagreeable nervous phenomena. Many asthmatics are more or less sensitive to iodids; the initial dose should, therefore, not be greater than 1 or 2 grains two or three times a day. The dose may be increased to 5 grains if the sputum continues thick and tenacious, but as little as  $\frac{1}{4}$  grain may suffice in sensitive patients. Benzyl benzoate is useful in only about one of twenty patients, but when it does work, it is of great value. Its routine trial in all asthmatics is, therefore, worth while. Finally, it is to be remembered that one is treating a patient, not a disease. Digestive disorders (often from too much medication), anemia, etc., must be recognized and properly treated. It is often a good plan to discontinue the drugs mentioned and to shift to tonic treatment: arsenic and iron will be found most useful.

**Relapses.**—Only too often “cured” patients do not stay “cured.” In fact, as a rule, we do not cure our patients in the sense of rendering them non-sensitive. Moreover, it is to be remembered that the underlying factor in allergic asthma is not merely hypersensitiveness, but sensitizability. Patients, therefore, can and do develop hypersensitiveness to new substances in a changed environment.

The chief known causes of relapses are: (1) Re-exposure to old causes, *e. g.*, the contact with horse-hair in a new mattress (thought by the patient to be wool). (2) Development of new sensitizations: the commonest are those to pollens and to house-dust in new surroundings. (3) Reinfection and (4) progressive nasal pathology. An acute rhinitis may light up a new sinus infection. Nasal polyps are notoriously prone to recur, and may block sinus drainage or reflexly produce asthma.

The patient who is the subject of a definite relapse should be handled as if he were a new patient. The whole history should be rechecked, and the details leading up to the relapse must be elicited—new dust exposures, change of occupation, or residence, new pets, altered diet. It is advisable that the phys-

ician inspect personally the patient's home and surroundings for possible causes of trouble that the patient might have overlooked. Skin tests should be made to cover the new exposures. Previous tests are to be repeated, for unfortunately skin reactivity is variable in degree and does not accurately parallel systemic reactivity. The skin test with a given substance may be strongly positive on one occasion and so slight or questionable on another as to be overlooked. It is quite possible, therefore, that on retesting an offending substance may be discovered that was missed at the first examination.

The nose and sinuses must be re-examined, both clinically and by *x*-ray. It is to be remembered that a sinus which has been subjected to operation is likely to have thickening of bone or mucous membrane and will therefore appear cloudy in the *x*-ray. Adequate surgery should be performed as indicated.

Fresh cultures should be made of nasal and bronchial secretions. Sensitization to bacterial protein probably occurs in some instances. The writer has, therefore, found it useful to follow the method of Thomas in performing intracutaneous skin tests with heavy suspensions (5,000,000,000 organisms to the cubic centimeter) of the various organisms isolated and using those which react positively to make a vaccine. Streptococci are the commonest offenders, but a variety of organisms, including the colon bacillus, may be found operative.

**Summary.**—Incompleteness of diagnosis and treatment is a common cause for failure in the treatment of bronchial asthma. Incomplete diagnosis may be traced to an inadequate history that fails to elicit essential etiologic facts or to an inadequate examination. To be complete, the examination must include skin tests for all possible sensitizing substances with which the patient comes in contact. The examiner must obviously have a thorough knowledge of the etiology of the disease. Nasal examination must be made both clinically and by *x*-ray, since neither method is adequate by itself. Incomplete treatment consists both in the failure to follow all therapeutic leads in a given case and also in the inadequate carrying out of each particular indication for treatment. In the latter connection the

commoner errors are failure really to avoid offending substances, and the inadequate treatment of sinus disease. Relapses are mostly traceable to re-exposure to old causes, to the development of new sensitizations, to reinfection, and to progressive nasal pathology. The patient whose disease has relapsed should be studied as if he were a new case, deserving of a new history and a complete re-examination.



## CLINIC OF DR. JOSEPH SAILER

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### REPORT OF A CASE OF PSITTACOSIS

MRS. M. L., aged forty-seven years, received from her husband in July a valuable gray African parrot, which seemed to have a bad cold. Mrs. L. nursed it devotedly, allowed it to feed from her mouth or to kiss her, and kept it continually by her. Mr. L. wrote to the New York Zoölogical Garden, and received a letter from an authority there expressing the opinion, from the symptoms that he had described, that the bird had psittacosis. These symptoms were fever, it felt hot, it was droopy, it would not eat, had severe diarrhea, its feathers were ruffled and fell easily, and it craved water continually.

Cultures were made from the parrot's stools, but only staphylococci and colon bacilli were recovered.

Mrs. L. had a severe headache on *August 26th*. On the *29th* she had a severe chill and aching in the limbs, followed by fever which rose to about 102° F. There was a violent frontal headache, and she was supposed to have influenza. On *September 3d* an area of consolidation was found in the upper part of the lower lobe of the right lung. Her temperature at this time ranged between 104° and 105° F.; the pulse was between 120 and 126; and the evening temperature was about 1 degree higher than the morning temperature. On *September 5th* and *6th* she had distinct chilly periods with a subsequent rise of temperature of more than 2 degrees. During the first ten days of her sickness there was no cough, a mild constipation relieved by magnesium citrate, moderate tympanites, and intense headache. On *September 5th* she complained of blurred vision, her hearing

was impaired, there was muttering delirium, and she lapsed into a condition of semiconsciousness. Occasionally she vomited small amounts of mucus which was not bloody, not even blood tinged. On the tenth day of the known fever she began to cough, but there was never expectoration.

Notes were made on *August 31st*. Her temperature was 104° F. for four days, the pulse was 120, and the respiration 30. There was consolidation of the right lower lobe.

On *September 7th* the physical signs were noted as follows: Temperature, 105° F.; pulse, 124; blood-pressure, 170/70. The skin was pale, with a yellowish cast; the lips and mucous membranes were cyanosed. Over the right lower lobe there was a patch of dulness, with bronchial breathing, bronchophony, and some crepitant râles. A systolic murmur was heard over the base of the heart, transmitted into the vessels of the neck. A pulse could be felt in the suprasternal notch. The spleen was not palpable, but the abdomen was slightly distended.

Several days later, *September 10th*, there was a second rise in fever, and an area of consolidation could be determined in the left lower lobe. Two days later the temperature began to decline by lysis, and reached normal on the fourteenth day.

On *September 7th* the urine contained albumin, 2 plus; many pus-cells; specific gravity, 1.011; and leukocytes, 10,400.

On *September 9th* there were 10,000 leukocytes, 82 per cent. of neutrophils, 18 per cent. of small lymphocytes, 2,800,000 erythrocytes, and the hemoglobin was 55 per cent. Blood agglutination showed typhoid negative and paratyphoid B positive. Culture from the feces was negative for typhoid.

The patient's husband refused to permit blood to be taken for a blood-culture. No sputum could be obtained. Unfortunately the patient's husband was so impressed by the agreement in diagnosis between the clinicians and the zoölogical expert, which occurred without the possibility of collusion, that he regarded all further tests as superfluous, and even sent the parrot away to die, to a place where its humerus could not be examined. We were told that the parrot had improved, and then died during a relapse.

The treatment consisted of the application of cocain and adrenalin to the mucous membranes of the nose. This promptly relieved the headache, and required only a few reapplications. Ammonium chlorid was given throughout the rest of the disease, and served very well. Later, as there was slight tenderness over the gall-bladder, olive oil was administered.

She complained of tenderness beneath the angle of the left scapula during convalescence. This was the last point at which consolidation of the lung was noticed. Her blood-pressure has remained high since the attack, and in September, 1928 was 180/104. Otherwise all tests were normal; these included the blood, the urine, which had a specific gravity of 1.005, the gastric contents, which showed free hydrochloric acid 10 and total acidity of 22, and the duodenal contents. Convalescence has been normal.

The case has been most imperfectly studied. This has been due to several causes: the distance the patient was from a large city supplied with laboratories, the unwillingness of the husband to have tests made, his satisfaction with the medical attention that his wife received, and his agreement with the diagnosis. It seems rather daring, therefore, to report this as a case of psittacosis.

The story of the recognition of this disease is of some interest. In 1892 two Frenchmen, Marion and Dubois, brought 500 parrots from Buenos Aires to Paris. Three hundred of these died during the voyage, and each arrived with 95. Marion went to live with his brother; he developed pneumonia and recovered, but his brother developed pneumonia and died. Dubois went to live with a family named Lievard. Dubois also developed pneumonia and recovered, but 7 members of his landlord's family had pneumonia and died. Providence did not seem to dispense justice according to ordinary human principles. Numerous neighbors were infected. The epidemic was so peculiar that Dujardin-Beaumetz was assigned to study it. He decided that it was a grippal infectious pneumonia. Others shared this opinion, so difficult is it to recognize a new disease. Peter regarded it as a typhoid of parrots transmitted from the



bird to the man. In 1892 Nocard found in the medulla of the humerus of one of the original parrots a bacillus which he called the bacillus of psittacosis, and which proved to be the cause of the disease. It has some affiliations with the typhoid bacillus. It has rarely been found in human patients.

The infected parrots are dull, motionless, sleepy, the feathers are ruffled, the wings droop, and the birds have diarrhea and no appetite. This condition lasts from eight to fifteen days. It appears to be a common vice for the mistress to permit the parrot to feed from her mouth, which greatly favors the transmission of the virus. In human beings the incubation lasts from seven to twelve days, and resembles that of typhoid fever, with more backache and pains in the limbs. There is also some facial edema, often around the mouth, much prostration, headache and epistaxis, and there may be nausea and vomiting. Chills are constant, the temperature reaches 104° F. in the evening, and there are morning remissions. After five days the stadium is reached, the patient becomes delirious, with irregular movements; the tongue is pasty; the appetite is lost, and thirst is constant. Vomiting is frequent, either of food or bile, there is slight tympanites, and either diarrhea or constipation. The spleen is usually palpable. Early in the disease the pulmonary symptoms are prominent, either bronchitis or lobar or lobular pneumonia developing. The urine is febrile. The mental symptoms are severe—delirium, hallucinations, carphologia, and subsultus tendinum. The stadium usually lasts for eight to ten days, and then, in favorable cases, recovery occurs by lysis. In the unfavorable cases the stupor becomes profound and the patient dies. In some cases death is due to the pulmonary lesion. Dieulafoy recognizes various types, but they are chiefly exacerbations of one or other of the chief symptoms. Particularly in the aged, or in the presence of complications, such as cardiac lesions or diabetes, is the prognosis grave.

In this case the diagnosis is based upon the history, the character of the case, which seems almost typical of the cases reported in Paris, and perhaps—although the diagnosis was made before we knew of it—upon the diagnosis of the condition of the

parrot, whatever this may be worth. Psittacosis is at least more reasonable than any other diagnosis, although the final bacterial diagnosis was not attained.

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# CLINIC OF DR. THOMAS FITZ-HUGH, JR.

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## HEPATO-UROLOGIC SYNDROMES

(a) Obstructive Jaundice and Nephritis

(b) Urologic Infections and Cholemia

THE following case-histories are presented as a group of complementary pictures illustrating several aspects of what appears to be a pathologic interrelationship between the liver and the kidney systems in certain of their respective disorders. It must be admitted at the outset that the nature and mechanism of this relationship cannot be clearly defined. Perhaps indeed it may be nothing more than an example of the truism that "disease of one organ affects the others"; or merely the dual effects of a common cause.

Whatever one's conclusions may be regarding the hypothesis, the facts of the case-histories will, I believe, prove of interest and clinical value.

The first 2 cases illustrate the apparently nephrotoxic effect of acute calculous common duct obstruction. The other 2 cases illustrate the apparently hepatotoxic effect of urinary tract instrumentation and infection. In the discussion which follows these case-histories the thesis is further developed that the liver and kidney stems may be more intimately related in certain diseases than is generally realized.

Case I.—Incipient Uremia Apparently Resulting from the Cholemia of Acute Calculous Common Duct Obstruction. Cured by Surgical Drainage.—Mrs. Z., age fifty years, was first seen 6/13/27 in consultation with Dr. Coffey. At this time patient had been ill for twenty-four hours with violent pain in the right upper abdomen, chills, and high fever. She had had several similar but milder attacks during the preceding twelve months which were attributed to pyelitis on account of the finding of pus in the urine. When seen by me the patient was apparently in a state of mild "shock" with low

blood-pressure, slight cyanosis, and marked tenderness and resistance in the right upper quadrant of the abdomen. Jaundice was not externally detectable, but the urine was loaded with bile-stained casts and pus and contained a cloud of albumin, a strong trace of bilirubin, and no sugar. A tentative diagnosis of acute, calculous, common-duct obstruction was made. On admission to the University Hospital the next day, 6/14/27, the leukocyte count was 20,700 with obvious jaundice, van den Bergh, direct immediate, indirect 6 units, and blood-urea nitrogen 34 mg. per 100 c.c. Blood-sugar was 120 mg., blood-calcium 8.7 mg. The patient was semistuporous and had sudden high peaks of fever. At operation, 6/15/27, Dr. Eliason found the gall-bladder and cystic duct packed with stones which by direct pressure and by contiguous lymphangitis had obstructed the common duct. The stones were removed and the gall-bladder drained. The patient made an uneventful recovery. At the time of her discharge, 7/9/27, the urine was negative except for a trace of albumin and 10 to 15 pus-cells per high power field. Blood-urea nitrogen had dropped to 14 mg. per 100 c.c. The specific gravity determinations (five in all) ranged from 1.009 to 1.016. Two prior determinations (May, 1927) by Dr. Coffey showed 1.023 and 1.018 urinary specific gravity. The patient at present (June, 1928) is perfectly well.

Here is a case of calculous cholecystitis and obstructive jaundice which was associated with (and I believe which *caused*) pyelonephritis and finally nitrogen retention. I am confident that this patient would have died of cholemia-uremia had not prompt surgical relief of the hepatic obstruction been performed (see Case II).

**Case II.—Fatal Uremia (and Diabetes) with Autopsy Findings of Clinically Unrecognized Hepatitis and Common Duct Cholelithiasis.**—Mrs. B. T., age forty-seven years, was admitted to the service of Dr. Stengel, University Hospital, on 9/30/27. Her history was that of recurrent gall-stone colic which began in 1924 and culminated in jaundice a year later when she was operated upon in this hospital (cholecystostomy with removal of about 50 gall-stones). Symptoms persisted, however, and on 1/17/27 a second operation was performed; this time more stones were removed from the gall-bladder and also from the common duct, which was drained in the usual fashion.

Convalescence was fairly satisfactory, but glycosuria and moderate hyperglycemia were discovered then for the first time. During the subsequent six to seven months the patient apparently had increasing diabetic symptoms and also complained of a great deal of dyspepsia and pain in the right upper abdomen. For several days prior to her last (present) admission to the hospital she had chills, fever, and some diarrhea and vomiting. Examination 9/30/27, semistuporous with acidotic breath. Leukocyte count 24,300, hemoglobin 120 per cent. Urinalysis: Albumin a trace, sugar strongly positive, urinary ketones, negative; occasional hyaline cast. Blood-sugar

0.483 per cent. Plasma CO<sub>2</sub> 38 vol. per cent. Blood-urea nitrogen, 174 mg. per 100 c.c.

In spite of the usual active treatment for diabetic coma (including intravenous glucose and saline and large doses of insulin) the patient died the following evening, 10/1/27.

The clinical diagnosis was diabetes and uremia, although Dr. Collins recorded his suspicion of "severe hepatitis related to former gall-bladder disease" when he first examined the patient on admission.

*Autopsy* (10/2/27) by Dr. George Robson (significant data only).

Liver, "fatty infiltration; marked parenchymatous degeneration; interstitial subacute hepatitis." Gall-bladder, "chronic cholecystitis."

Common duct, "dilated to size of a lead pencil and contains three small faceted stones which lie loose in its lumen."

Pancreas, "fatty infiltration, chronic interstitial pancreatitis."

Kidneys, "acute diffuse glomerulonephritis, profound tubular degeneration."

It is impossible to state with certainty just which of these factors actually caused the death of this woman, but the inference seems almost unescapable when one reviews her story that the central factor of her trouble was gall-stones; hepatitis, nephritis, and pancreatitis being secondary. Death was apparently due to uremia, which I would ascribe to the repeatedly and more or less continuously nephrotoxic action of calculous choledocholithiasis with obstructive hepatitis.

**Case III.—Acute Cholemia Induced by Urethral Instrumentation and Subsequent Urologic Infection in a Patient with Presumable Pre-existing Unrecognized Hepatic Disease.**—Mr. X., age forty-three years, was referred 3/8/25 by Dr. D. C. Smith of the University of Virginia who had treated the patient in November, 1924 for luetic mediastinopericarditis which developed one year after acquisition of the primary lesion. At my examination in 1925 the patient presented no subjective or objective evidence of disease of any kind except that his blood Wassermann was weakly positive (cholesterinized antigen ++, alcoholic antigen +, Kolmer ++).

Under treatment by bismuth injections together with mercurial inunctions and iodid by mouth the patient continued well and his blood Wassermann has since been repeatedly and persistently negative. He was given a course of mercury and iodids every six months for the past two years, but received no arsenicals. In January of this year (1928) he reported a urethral discharge which appeared after alcoholic excesses and extramarital relations. He had had recurrent urethritis under similar circumstances before; in fact, every few years since his first niesserian infection eighteen years ago. I referred him to a urologist for treatment. After several weeks of conservative management without improvement the urologist felt that urethral dilatation should be tried. Twenty-four hours following this procedure the patient had chills and fever and marked dysuria and developed increasing pain and swelling of the left testicle. He apparently went to bed for a few days without medical attention. I saw him a week after instrumentation (3/6/28), at which time his temperature was 102° F., his left epididymis was swollen

and tender, and his urine was apparently very bloody. To my surprise when the urine was examined microscopically no blood-cells were present. There was a great deal of pus. Test for occult blood was negative. Test for bilirubin was strongly positive. There was a light cloud of albumin and some dark granular bile-stained casts. This was my first intimation of jaundice, and in spite of the urinary proof of biliary obstruction there was no obvious jaundice of the skin and eyes until several days later. The jaundice then steadily increased, the stools became alcoholic, and the urine remained heavily clouded with bile and pus. The patient became somnolent and at times delirious. He complained of pruritus, extreme weakness, and nausea. There was some tenderness along the liver edge which was barely palpable. The spleen was not enlarged at any time. The patient was in this serious condition with fever, chills, jaundice, and dysuria for three weeks, when he began to improve. Temperature subsided and urinary disturbance and epididymitis diminished, but jaundice continued unabated.

On 4/6/28 he was admitted to the University Hospital, where Dr. Pepper saw him in consultation with me. At this time the blood Wassermann was again negative, the stools were acholic, the urine showed a cloud of albumin, many casts, 25 pus-cells per high-power field, 4 to 6 red blood-cells per high-power field, and a strongly positive test for bilirubin. Blood-count, blood-urea nitrogen, and blood-sugar all normal. The blood van den Bergh was direct—delayed, indirect 4.5 units. The liver edge was soft, slightly tender, non-nodular, and extended 2 cm. below costal border.

Our diagnosis was influenced by the recent report of Dourmashkin.<sup>1</sup> We felt that this case belonged in the same group: a patient with presumable hepatic disease (heretofore symptomless and due to lues or alcoholism or both) was precipitated into severe cholemia (of hepatitis) induced by instrumentation of the urethra and subsequent urinary tract infection.

The patient gradually recovered and jaundice finally disappeared, so that it was no longer discernible seven weeks after onset. When last examined, 4/27/28, the urine was free of bile and generally negative except for a few pus-cells.

**Case IV.—Gestational Toxemia with Intercurrent(?) Pyelonephritis, and Consequent(?) Cholemia. Recovery Following an Abortion.**—Mrs. R. A., aged twenty-four years, was admitted to obstetric service of Dr. Bachman, 5/6/28, with well-marked early gestational toxemia which had begun about the fourth week of pregnancy and had increased to the present time (now four and one-half months pregnant). In addition to the persistent vomiting and headache of over three months' duration the patient had had for the past few days marked lumbar and pelvic pain, urinary frequency, dysuria, chills, and fever.

On admission the leukocyte count was 15,000 and the urine was loaded with pus. On 5/8/28 cystoscopy confirmed the diagnosis of bilateral pyelitis and hydronephrosis with cystitis. The following day ureteral catheterization and lavage of the renal pelvis were performed. Two days later, 5/11/28, jaundice was first noted. On this day the blood-urea nitrogen was 54 mg. per 100 c.c.; van den Bergh direct, immediate, indirect 5 units. The leuko-

cyte count had jumped to 58,400 with hemoglobin of 35 per cent. The next day the patient aborted.

On 5/13/28 I was asked to see her because of the blood-picture which had raised the question of leukemia. When seen by me the leukocytes numbered 65,000 per cubic millimeter with a differential of 88 per cent. neutrophils, 4 per cent. lymphocytes, 8 per cent. myelocytes, and many nucleated erythrocytes. The hemoglobin was 37 per cent. (Sahli). Jaundice was well marked. The liver and spleen were not enlarged. No adenopathy. Blood-cultures negative, blood Wassermann negative. The diagnosis was obviously severe sepsis of urinary tract origin with leukemoid blood reaction due thereto, together with obstructive jaundice, which I interpreted as a result of hepatitis. The patient's history contained no suggestion of previous biliary tract disease. It was my opinion that the urinary tract infection (and instrumentation[?]) precipitated cholemia on the basis of mild pre-existing liver damage incident to gestational toxemia. The patient made an uneventful recovery and is now reported entirely well except for slight pyuria.

**Discussion:** (1) **The Apparently Adverse Effects of Hepatic and Biliary Tract Disease on the Kidneys.**—That cholecystitis may be a causative focus of infection in the production of nephritis is generally believed. A particular form of this relationship—the occurrence of hematuria in patients with gallstones—has recently been emphasized.<sup>2</sup> Furthermore, it is commonly known that albuminuria and cylindruria are frequently found in obstructive jaundice. That acute calculous common duct obstruction may apparently precipitate a patient into true (azotemic) uremia is, however, not generally realized. Case I illustrates an early and remediable phase of such a condition, while Case II is, I believe, fundamentally its fatal end-result.

Whatever the mechanism may be—whether bile-salts, bile-pigments, infection, or other toxemia—the fact remains that acute calculous common duct obstruction is definitely nephrotoxic. The urine of such patients, and also the urine of those with acute catarrhal jaundice, usually shows heavy traces of albumin, various casts, and often microscopic pus and blood. Of 25 consecutive recent cases of acute catarrhal jaundice in the University Hospital the records show that 12 had a cloud of albumin, 11 had a faint to heavy trace, and only 2 had less than a faint trace of albumin during the early stage of their jaundice. These cases were for the most part healthy young



adults. All recovered after the usual mild course characterized by little or no fever and no leukocytosis. Similarly, of 12 consecutive cases of calculous common duct obstruction, 10 have albumin in amounts from a heavy trace to a cloud during acute manifestations of the condition. Later on apparently the urine may clear up with subsidence of acute symptoms even though partial or complete ductal obstruction persists.<sup>3</sup> This, together with the fact that experimental obstructive jaundice (ligation of common duct in animals) does not produce much albuminuria,<sup>4</sup> would suggest that infection is probably the chief factor in producing the albuminuria of calculous and catarrhal jaundice. It is my impression, however, that if infection is the chief factor it is more peculiarly nephrotoxic than similar infections elsewhere and is augmented in this nephrotoxic action by something dependent upon its location in the biliary tract.

The nephritis (or nephrosis[?]) of acute obstructive jaundice does not, of course, last long enough to produce low fixation of urinary specific gravity; nor does it, as a rule, produce azotemia. That nitrogen retention does occur, however, is illustrated in Cases I and II. The latter case is also noteworthy in that high blood-urea nitrogen was present in spite of the fact that autopsy revealed marked and wide-spread liver disease.<sup>5</sup> It should be further stated that in neither of these "cholemic-uremic" cases (I and II) was there any other cause for high blood-urea nitrogen figures—*i. e.*, no alkalosis from the medication and no hypochloremia from the prolonged vomiting or diarrhea.<sup>6</sup>

Apparently marked albuminuria does not result from the so-called acholuric (hemolytic) familial jaundice. It does occur, however, intermittently in cases of syphilis and carcinoma of the liver with jaundice—probably varying directly with periods of hepatic obstruction and secondary infection in the bile tracts. In "postarsphenamin jaundice" the urine exhibits less albumin and fewer casts than it does in comparable stages of acute catarrhal jaundice—another point in favor of the factor of infection as the chief cause of the nephritis of jaundice. Acute yellow atrophy of the liver is characterized by a very marked

nephritis—the etiology and significance of which are still much debated.

**Discussion: (2) The Apparently Adverse Effect of Renal and Urinary-tract Disease on the Liver.**—Credit for first calling attention to this relationship belongs to Dourmashkin.<sup>1</sup> His report concerns 3 cases of cholemia apparently induced by and “following instrumentation of patients having obstructive lesions of the urinary tract with a coexisting hepatic cirrhosis.” I have recently seen 3 such cases and have reported 2 of these above (Cases III and IV). Here again the mechanism is uncertain, but infection would seem to be the most likely. Patients with frank hepatic cirrhosis are notoriously “bad risks” for any sort of trauma. In 2 of my cases, however, and in one of Dourmashkin’s the “cirrhosis” was by no means “frank.” It was so mild indeed as to be unrecognizable, and its existence was inferred more from the course of events and from etiologic probabilities than from any pathognomonic demonstration. Whatever the mechanism, it would seem wise to bear in mind the warning that “dangerous possibilities may result from instrumentation of patients suffering from hepatic cirrhosis.”

What suggestions can we find, in the light of these cases, for help in solving the much debated problems of nephritic *versus* hepatic types of gestational toxemia? Certainly no help of great importance, and yet Case IV *is* suggestive. Was the toxemia here of nephritic or hepatic type? It seems to me it was *both*. May not at least some of these gestational toxemias more properly be viewed as belonging in this group of combined hepatonephric disorders which urgently await clarification through future research?

The work of Andrews<sup>7</sup> and his collaborators<sup>8</sup> would seem to be an entering wedge into this problem. These investigators have shown that some of the albuminuria of experimental uremia is actually liver protein in the urine. As pointed out in recent editorial comment<sup>9</sup> on this work, “it is suggested that in nephritis a disturbance of the mineral balance causes cellular disintegration to such an extent that protein leaks from the great parenchymatous organs into the blood and is excreted” in the

urine as "foreign protein." Such passage of foreign protein in the urine is known to render the kidneys more permeable to blood proteins. Thus we have one possible explanation of a mechanism whereby liver disintegration may produce albuminuria and whereby nephritis may cause liver disintegration.

**Summary and Conclusions.**—Four cases are reported illustrating (1) the apparently nephrotoxic effect of acute hepatic obstructions with biliary tract infection, on the one hand, and (2) the apparently hepatotoxic effect of certain urinary tract disturbances (instrumentation and infection) on the other. It is further suggested that a more intimate relationship exists between the liver and kidney systems in certain diseases than is generally realized.

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# CLINIC OF DR. DAVID A. COOPER

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### PRIMARY CARCINOMA OF THE LUNG

THAT primary carcinoma of the lung is increasing out of proportion to the general increase of cancer is accepted by most observers.<sup>1, 2, 3</sup> Prior to the past ten or fifteen years it was considered a rare condition, forming about 1 per cent. of all cancers. Even as late as 1917 McMahon and Carman<sup>4</sup> called it a rare disease. Recent reports show that the incidence of primary carcinoma of the lung is from 5<sup>5</sup> to 8 per cent.<sup>6</sup> of all cancers. In the past two years, in the private practice of Dr. David Riesman, there have been observed 5 proved cases. It is, perhaps, worth while to stress its importance, giving a brief summary of the prevailing ideas concerning the causative factors, pathologic types, symptoms, and diagnostic measures.

Primary cancer of the lung occurs about three times as often in males as in females, and in about 95 per cent.<sup>7</sup> of the cases after the age of thirty, however, it has been reported in younger individuals. Micheler<sup>8</sup> reports a case in a girl of seven; Horn,<sup>9</sup> in a girl of eighteen, and Weiner,<sup>10</sup> in a woman of nineteen years. As to race and nationality it appears that the Hebrew race is, at least in our experience, more likely to develop it than others. This is also the opinion of Dr. H. K. Pancoast, who considers it an important point in the differential diagnosis. Whether this is due to some inherent racial characteristic or to the frequency of the occurrence of chronic pulmonary infection in this race cannot be answered. Different observers vary in their reports as to whether the right lung or the left lung is involved more frequently. Ferenczy and Matolcsy<sup>11</sup> give the right lower lobe as the most frequent site and explain its preference by its being

more subject to injury due to its course and the diameter of the bronchus.

Chronic irritation appears to be the most important etiologic factor, due either to the inhalation of dust particles and irritating fumes, or the presence of chronic pulmonary infections. The occurrence of pulmonary cancer in miners of ores containing arsenic or cobalt has been called to attention by Arnstein<sup>12</sup> in 1913. Apparently this is not applicable to miners generally because Pancoast, in his studies on pneumoconiosis, in which a thousand miners at various stages of the disease were studied, did not find a single case of carcinoma of the lung. The increasing use of tar preparations on roads and roofs has been considered of importance by some, as it has been shown experimentally that preparations of tar will cause a proliferation of the bronchial epithelium.<sup>13</sup> The inhalation of exhaust from automobiles and excessive smoking have been named as etiologic factors. Among the chronic infections tuberculosis is the most important (Ewing<sup>14</sup>). Of the 31 cases reported by Wolf,<sup>15</sup> 13 showed tuberculosis. This probably accounts for its predilection for the upper lobes reported by some observers. However, one of our cases showed bilateral apical evidence of tuberculosis with a bronchial carcinoma involving the left lower lobe. This would lead one to say that the tuberculous disease *per se* is not the factor, but that fibrosis and distortion of the structure of the lung which occurs in healing with its secondary infection is the more important. In a similar way we have the condition in the bases of the lungs in chronic bronchitis and bronchiectasis, and for this reason consider it of almost equal importance as an etiologic factor. However, the general incidence of tuberculosis is greater than that of bronchiectasis. In cases of this type as well as in tuberculosis there are evidences found of changes in the bronchial epithelium that are generally considered as pre-cancerous, namely, overgrowth and metaplasia of the bronchial epithelium. This cellular alteration may lead to a lack of tissue restraint. With the increase of pulmonary carcinoma since 1917 the influenza epidemic has been given an important place as an etiologic factor. Here again, due to the chronic bronchitis

which persisted after the influenza, we have a low-grade type of infection with the associated changes in the bronchial mucosa. This as a cause for the present increase was predicted by Winternitz in 1920.

Primary carcinoma may occur anywhere along the bronchial tree and out in the parenchyma of the lung. However, 80 to 90 per cent. (87 per cent., Passler<sup>16</sup>) are of bronchial origin. There are three groups recognized according to their histogenesis (Ewing<sup>14</sup>). Those arising from: (1) Bronchial epithelium; (2) bronchial mucous glands; and (3) alveolar epithelium. The specific features of the disease belong mostly to the early stages. It is not possible to separate all advanced cases, especially those of a highly malignant character. Carcinoma arising from the bronchial epithelium begins at or below the bifurcation and extends along the bronchial mucosa with fungating growths into the bronchus, but seldom produces a diffuse tumor of the lungs. By growing into the bronchus and plugging, it will produce atelectasis, and in some abscess formation distal to the lesions will result. The tumor process may extend to the pleura and frequently there is a serous or bloody effusion. Carcinoma arising from the mucous glands have rather characteristic features. They are limited chiefly to the submucosa leaving the bronchial epithelium intact with a tendency to produce a stenosis of the bronchus. Histologically they have the structure of a glandular carcinoma. The type that arises from alveolar epithelium is either multiple and nodular or diffuse. In the nodular form one or both of the lungs may be the seat of nodules varying in size; these may be solid or cystic and may show areas of necrosis. In the diffuse form a lobe or an entire lung may show diffuse infiltration. The types of cells vary from cuboidal and cylindrical to flat. Metastasis varies with the degree of malignancy of the tumor, but is usually wide-spread. In 374 cases reported by Adler<sup>7</sup> all but 33 showed evidence of metastasis, the regional lymph-nodes and liver being the most frequent sites. However, few organs fail to appear as possible sites for metastasis. The heart is more often involved than in any other malignant growth.

The onset is very insidious. Most frequently the first symp-

toms to be noticed are persistent unexplained cough and indefinite dull pain in chest. Expectoration is variable and may or may not be blood streaked. The "currant-jelly" sputum spoken of in text-books is rarely seen except late in the disease. However, one of our cases, Mr. H. S., a Russian Jew, aged sixty-nine, had had cough and expectoration for years, but considered himself well until about one year ago, when he had a severe hemoptysis (several basins of blood). Since that time he has had increasing weakness and shortness of breath—with cough and expectoration which has recently been bloody. This patient had a growth involving the lower left lobe which did not respond to Roentgen-ray treatment. Another type of onset is shown in Mr. L. K., aged forty-six, Russian Jew, who came in complaining of dyspnea and substernal pain of one month's duration. On examination it was found that he had an effusion in the right chest, the underlying cause of which was a carcinoma of the right lower lobe. Another case, Mrs. F. S., a Russian Jewess, aged sixty-two, was admitted with the chief complaint of cough and pain in chest of one month's duration, with slight mucous expectoration that had never been blood streaked. Roentgenologic and bronchoscopic studies showed a carcinoma of the lower left lobe. The disease progressed rapidly in spite of Roentgen-ray treatment, and the patient died in about two months.

Features that have impressed me in the cases observed are the absence of symptoms early in the disease and later the marked prostration out of proportion to the amount of involvement. The character of the onset will often suggest the type of lesion, namely, a lesion well out in the parenchyma of the lung will have an insidious onset. The most frequent symptom of this group will be dull indefinite pain in the chest; whereas a lesion arising from the larger bronchi will most likely cause cough and blood spitting. Fever and sweats are usually associated with secondary infection. Loss of weight to any appreciable degree has not been found in any of our cases. From a symptomatic standpoint a persistent cough with pain in the chest and blood spitting in an individual over thirty-five should lead us to consider carcinoma of the lung.

Too often the signs that can be elicited on physical examination are negligible. The chest findings are quite within normal limits early in the disease, and late in the disease are not characteristic. The finding of a supraclavicular node will give one a lead, but is indicative of metastasis. Frequently a pleural effusion will mask the underlying intrapulmonary lesions. With signs suspicious of fluid a diagnostic thoracentesis is indicated.



Fig. 186.—Parenchymal type of carcinoma of the lung. Patient was a Russian Jewess, age sixty-six years, who complained of persistent pain in the right upper chest, front and back, for seven months. About the time of the onset she had a febrile attack and was diagnosed pneumonia, but signs persisted and pain increased.

The fluid usually has the characteristics of a transudate and may or may not be bloody, dependent upon the extent of the lesion; when the pleura is involved it is usually bloody. When the lesion is in the parenchyma of the lung the percussion note is dull to flat, and at times a peculiar "stony" flatness is present. Breath-sounds are usually diminished, but may be bronchial.



Often with a central lesion the signs will be those of partial or complete bronchial obstruction. Râles may or may not be present.

The laboratory findings are usually of little value. The blood usually shows a secondary anemia with the presence of a leukocytosis dependent on secondary infection. The sputum in rare instances late in the disease may show fragments of tissue.



Fig. 187.—Bronchial type of carcinoma of right lung in a woman aged thirty-eight years. At the time of this film the patient had had cough and expectoration for one month. She later developed abscess due to obstruction which was followed by empyema. Bronchial carcinoma beginning in the right hilum.

The importance of Roentgen studies in chest diseases cannot be too strongly emphasized—in fact, some “chest men” say that no chest examination is complete without roentgenologic and fluoroscopic studies. The roentgenologic findings in early primary carcinoma of the lung are variable but fairly characteristic in

most instances according to Kirklin and Patterson.<sup>17</sup> They describe two types—the parenchymal and the bronchial. The parenchymal begins as a definitely localized nodule in the parenchyma of the lung. It is an irregular area without increased density of its margin and with infiltrating edges. There



Fig. 188.—Bronchial type of carcinoma of the lung. Patient was a Russian Jewess, age sixty-two years. For several months there had been a dry, non-productive cough that had gotten worse in the past month with the development of pain in her left chest. Physical signs were dullness and diminished breathing over the left base—a small serous effusion was found on tapping. Films show evidence of healed tuberculosis in addition to the left basal lesion. Bronchoscopy showed an adenocarcinoma of the left main bronchus. Patient died two months later in spite of Roentgen-ray treatment.

is also a lobar type of parenchymal tumor which shows a diffuse clouding of an entire lobe that is less characteristic.

The bronchial type appears as a mass at the hilum with the appearance of infiltrating toward the periphery of the lung. This appearance may be actual or due to atelectasis. These

characteristics are often masked by an overlying effusion or by secondary infection.

Bronchoscopic examination in the bronchial type is usually definite and the diagnosis can be proved by biopsy. There are few contraindications to its use, and it should be used in all cases, as it gives valuable information.

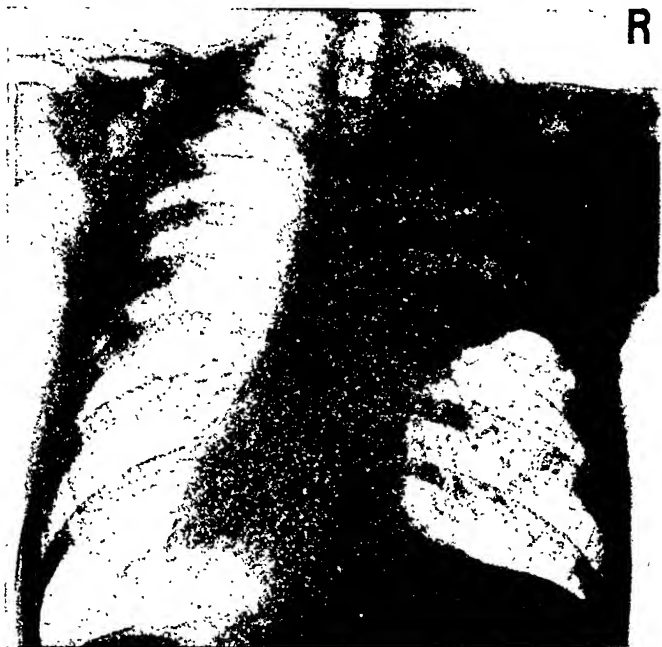


Fig. 189.—Bronchial type of carcinoma of the right lung with obstruction and atelectasis of the upper lobe. The patient was a man aged fifty-one years. Symptoms were cough, expectoration, and pain in chest. Bronchoscopic examination revealed a stenosis of right upper lobe bronchus.

In cases that are complicated with an effusion the withdrawal of the effusion and the induction of a pneumothorax followed by roentgenographic studies have been of value in several instances. Needling the lung and in this way obtaining tissue has proved a diagnosis in one case, and is not a dangerous procedure if done with care.

In differential diagnosis pulmonary tuberculosis is most

often confused. The age incidence is of value, as tuberculosis occurs more frequently in younger adults. The histories may simulate each other closely. In tuberculosis the physical signs are usually apical and bilateral. A positive sputum proves the presence of tuberculosis. However, the two may and often do occur together, but in tuberculosis the roentgenologic evidence is characteristic. I have recently had the opportunity to observe such a case in which the diagnosis was made on roentgenologic findings and confirmed at autopsy.



Fig. 190.—Lateral view of Fig. 189.

Lung abscess in our experience is most frequently confused; here the history may or may not be of value. There are often secondary abscesses peripheral to a malignant bronchial obstruction that will confuse the clinical picture and the roentgenologic findings. Bronchoscopic examinations will usually settle the question. Bronchiectasis may simulate carcinoma of the lung,

but the history is usually of much longer standing, often dating from childhood. The physical signs are usually bilateral; however, it has been shown that carcinoma may develop in patients with bronchiectasis. Bronchoscopic studies are our only hope for differentiation.

Metastatic tumors usually give a history of probable malignancy in some other organ with symptoms and signs of pulmonary disease. The roentgenologic features of the metastatic nodules are definite; then, too, metastatic lesions are usually multiple.

Without a definite history a foreign body may give signs and symptoms that would suggest a growth. Roentgenologic examination is definite in cases of bronchial obstruction, but with a non-opaque foreign body the differentiation can only be made by the bronchoscopist.

Gumma of the lung is a rare condition, but may simulate closely a carcinoma. With a positive Wassermann a therapeutic test is justifiable.

Benign tumors and cysts give a history of long standing without evidence of progression. The roentgenologic findings are characteristic, namely, a single clean-cut lesion remaining the same size on repeated examinations.

Mediastinal tumors causing pressure on a bronchus may give symptoms and signs and even Roentgen evidence of cancer of the lung. Here again the bronchoscopist is the final court of appeals. Aneurysms can usually be differentiated on physical findings and fluoroscopic studies.

The prognosis at present is grave and our only hope of improving it is early diagnosis followed by intensive and radical treatment.

Intensive Roentgen therapy is generally accepted as the best and most conservative form of treatment. A number of cases have been reported in the literature in which it has undoubtedly prolonged life, and rare cases that could be said to be cured or in which the lesion has disappeared under treatment. However, in my limited experience it has not come up to expectation. In the 23 cases that have been treated by Roentgen rays at the

University Hospital, 20 are dead, one cannot be traced, and of the 2 cases known to be alive, one case had the following biopsy report: "Inflammatory tissue probably malignant." This lesion cleared up on Roentgen-ray treatment. The other case, which is under my care at present, has not been proved definitely as a carcinoma.

Surgery is more radical, and there are few cases diagnosed early enough to be amenable to surgical treatment. But there are cases reported in which lobectomy was performed with good temporary results. Tumors that are massive may be treated by the cauterization method developed by Evarts Graham.

Bronchoscopic removal is possible only in rare instances, but when feasible should be done. There are a few cases on record with apparent cure following endoscopic removal.

**Comments and Conclusions.**—That pulmonary carcinomata are apparently increasing in frequency is generally accepted. There are many theories given as to the cause, but none proved. Chronic irritation is probably the most important known factor. The history and physical findings are indefinite in most instances. Bronchoscopic and roentgenologic findings are definite in most instances. Definite diagnosis is important because of the grave outlook in this condition. The hope of cure lies in its early recognition. This can be accomplished by a realization of the increasing frequency of this disease and a close co-operation among the practitioner, the roentgenologist, the bronchoscopist, and the surgeon.

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# CLINIC OF DR. JOSEPH T. BEARDWOOD, JR.

## PRESBYTERIAN HOSPITAL

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### DEXTROSE TOLERANCE TEST: ITS USES AND DANGERS

WE have chosen for today's clinic 3 cases illustrative of the value and also the danger of the dextrose tolerance test in conjunction with diabetes. This test was first used and described by Jacobsen about fifteen years ago, at which time he gave varying quantities of sugar to patients suspected of being diabetics. The urine was tested at intervals of thirty minutes and the appearance of sugar after the first specimen considered a positive sign of diabetes. He also used the test in conjunction with pituitary disease. With the introduction of modern methods of testing blood-sugar by Folin and Wu, the routine of the test was changed and the blood-sugar determinations were made before the administration of the sugar and at intervals thereafter. This test has been used as an adjunct in the diagnosis of numerous conditions. Among those in which there is decreased tolerance aside from frank diabetes, the following may be mentioned:

#### *Medical:*

1. Prediabetic conditions.
2. Pituitary disorders.
3. Hyperthyroidism.
4. Carcinoma of genito-urinary tract.
5. Cirrhosis of the liver.
6. Arthritis.
7. Hypertension.
8. Nephritis with urea retention.

#### *Gynecological and obstetrical:*

1. Pregnancy.
2. Endocrine imbalance.



*Neurological:*

1. Various mental diseases.
2. Myasthenia gravis.
3. Lower motor neurone disease.

*Ophthalmical:*

1. Cataract.

*Surgical:*

1. Buerger's disease.
2. Raynaud's disease.

*An increased tolerance is found:*

1. Addison's disease.
2. Hypothyroidism (certain cases).

A normal curve is obtained in renal diabetes, and this is one of the most important uses for the tolerance test.

The question as to whether in these conditions, aside from prediabetic and pituitary cases, the height of the curve is dependent upon the ability of the body to oxidize dextrose as it is in the diabetics or whether some other circulatory element enters into it, is still a disputed one. Recent work seems to indicate that possibly the factor of vasomotor constriction in various parts of the body may be a factor. In no disease except diabetes is the curve itself pathognomonic.

The exact technic of the test varies in the different clinics and with the different men, the chief variations being the amount of dextrose employed. The average amount is between 100 and 125 gm. of dextrose, which is usually given by mouth, in 300 c.c. of water flavored with lemon, after a twelve-hour fast, the blood-sugar and urinary determination being made before the sugar is administered and determinations made after thirty minutes and then at intervals of one hour, until three hours have elapsed. In some cases the dextrose has been administered intravenously, the most recent being the test for toxicity of pregnancy.

The technic as presented in the cases here has been that outlined above, except that 1.75 gm. of dextrose per kilo body weight has been used. It is pointed out by some men, particularly by Gray, that as much information in diabetes can be obtained by using a "50-gm. meal," that is, a meal containing

50 gm. of carbohydrates and ascertaining the blood-sugar at the end of two hours. This is probably true in cases of diabetes, but, of course, would have no value in other conditions named. It is probably the safest test to use in all cases suspected of being diabetic because, first, the patient is more willing to take two shredded wheat biscuits and 3 ounces of cream, which contains approximately 50 gm. of carbohydrate, than the large doses of

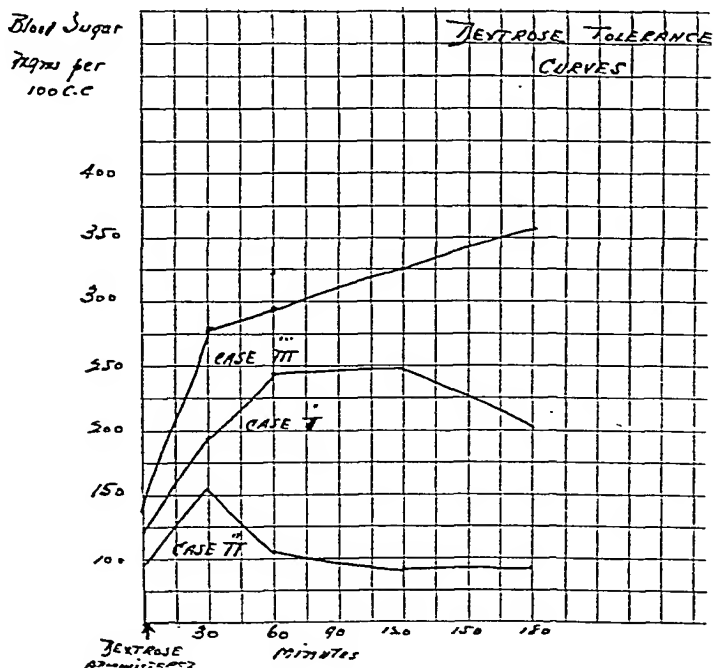


Fig. 191.—Normal curve (Case II). Mild diabetes (Case I). Moderately severe diabetes (Case III).

dextrose; secondly, there is not the danger of breaking the tolerance by throwing an increased load on the pancreas; thirdly, as a disciplinary point, the fact that the doctor at one time or another is willing to give them large doses of sugar may lead the weak-willed diabetic to break his diet with rather unfortunate results.

Of the 3 cases which I am showing you today, the first illus-

trates the mild type of diabetes, which might escape detection if we depended on one blood-sugar test and repeated examinations of the urine.

Case I.—Mrs. K., age forty-five years, whose chief complaint was ready fatigue and some loss of weight. In studying her in the medical clinic it was found that she had a blood-sugar of 150 mg. and she was referred to the diabetic clinic. She was not admitted to the house, but she was placed on a standard maintenance diet in the clinic. After a period of two weeks it was found that her blood-sugar ran between 120 and 126 with, of course, no urinary sugar. It was decided to do a sugar tolerance test to determine if the patient was a true diabetic, the result of which is as follows:

Fasting.	Blood-sugar. 124	Urinary sugar. 0 per cent.
Dextrose administered.		
30 minutes after dextrose.....	191	0 "
60 minutes after dextrose.....	238	1 "
120 minutes after dextrose.....	243	2.5 "
180 minutes after dextrose.....	210	5 "

This case is progressing very satisfactorily on a liberal maintenance diet. Her blood-sugar has remained constantly below 120 mg. and possibly she is the type of patient on whom a qualitative restriction of the diet would be sufficient. She illustrates the type on whom the test is the greatest value. In all probability, had she not been tested, she would have continued with an unrecognized, mild diabetes until some infection or other precipitative factor caused a sudden breakdown and a diabetic condition which only could have been controlled by rather rigid treatment and possibly the use of insulin.

Case II.—E. O'N., age seventeen years. Patient gave a history of excessive carbohydrate intake extending over some years, enuresis, polyuria, and polydipsia. He was sent to the clinic with a diagnosis of diabetes. Blood-sugar taken outside the clinic was reported as 154. He was admitted to the ward for standardization. While in the house his fasting blood-sugar ran from 95 to 105 on a standard maintenance diet and it was decided to do a sugar tolerance test, with the following results:

Fasting.	Blood-sugar. 95	Urinary sugar. 0
Dextrose administered.		
30 minutes.....	154	0
60 minutes.....	115	0
120 minutes.....	95	0
180 minutes.....	95	0

This is a normal curve and, of course, rules out the possibility of his case being one of diabetes.

Case III.—Mrs. M. R. White woman, age fifty-four years. In the routine studies in cardiac clinic a blood-sugar determination was made because patient complained of rather general neuritic pains and was found to be 200. She was admitted to the ward for standardization. After some days on standard maintenance diet, blood-sugar ranged from 125 to 140, and sugar tolerance test was done, with the following results:

Fasting.	Blood-sugar.	Urinary sugar.
	135	0 per cent.
	Dextrose administered.	
30 minutes.....	278	0 “
60 minutes.....	294	0.1 “
120 minutes.....	325	2 “
180 minutes.....	357	3.3 “

This patient continued to have hyperglycemia and glycosuria on the same maintenance diet which had before kept her controlled. She required 25 units of insulin a day to bring her back to normal, and she was compelled to take insulin in decreasing doses over a period of four months. Fortunately, she now is well-controlled without insulin, and has again regained her tolerance. In this case we see the danger of excessive carbohydrate feeding in mild well-compensated cases of diabetes mellitus. A rather interesting thing in this case is that while she had the hyperglycemia she was partially decompensated.

Great care should be exercised in all doubtful cases and a 50-gm. meal used in cases of this type. The 50-gm. meal has the advantage that the average practitioner can have his patient take such a meal as outlined above and make a blood-sugar determination within two hours. This involves no great loss of time and has the additional advantage that only one blood-sugar determination is necessary.

The dextrose tolerance test is a laboratory procedure of great value, and should be used in cases of suspected diabetes and also as an adjunct in the diagnosis of some of the above conditions.



## PREPARATION OF DIABETICS FOR SURGERY

THE subject of today's clinic is the preparation of diabetics for surgery, but before presenting and briefly discussing the illustrative case we will consider the question and outline the course which we usually follow in the clinic.

The diabetic as a surgical risk can now be placed on the same footing as the non-diabetic individual. The mortality among the surgical diabetics before 1922 was 33 to 50 per cent., but since that time it has been decreased until now it compares favorably with the rate among non-diabetics.

This remarkable improvement in mortality has resulted not alone from the introduction of insulin, but as a result of a better understanding and more accurate treatment which we have learned in conjunction with its use.

In operations of election, known or suspected diabetics should be admitted to the house, for five to ten days before the operation, for standardization; by this we mean rendering of the urine sugar free and reducing the blood-sugar within normal limits, with or without the use of insulin, at the same time keeping the patient on a standard diet, or in some cases a slightly subnormal one as far as the caloric intake is concerned.

In calculating the "standard diet" we allow  $1\frac{1}{4}$  gm. of carbohydrate per kilo of body weight, 1 gm. of protein per kilo, and fat in sufficient quantity to make up the caloric requirement which we consider to be 25 calories per kilo of body weight. So that in the case of a patient weighing 60 kilograms, the calculation would be as follows:

For carbohydrate	$60 \times 1\frac{1}{4}$	= 75 gm. of carbohydrate	= 300 calories
For protein	$60 \times 1$	= 60 gm. of protein	= 240 "
			<hr/>
			540 "

Caloric requirement  $60 \times 25 = 1500$  calories.  $1500 - 540 = 960$  calories to be obtained from fat.  $960 \div 9$  caloric value gm.

of fat = 106 gm. fat. So that the complete formula would be carbohydrate 75 gm., protein 60 gm., fat 106 gm. This ration will give a safe ketogenic, antiketogenic ratio. In cases in which the blood chemistry shows a tendency to acidosis, the above formula may have to be modified and a smaller amount of fat used and the carbohydrate proportionately increased.

The patient should be kept on the above diet for three to five days, and if laboratory findings are still above normal insulin should be used in sufficient amount to control the hyperglycemia. Once this is normal for forty-eight hours the patient is ready for operation.

It is of the utmost importance that once the carbohydrate balance is established, that it be maintained. To meet this requirement it is necessary that the patient be given the same amount of carbohydrate in twenty-four hours that he has been getting preoperatively and, of course, the same amount of insulin.

The glucose may be administered by mouth diluted with water or orange-juice or oatmeal gruel. If this is inadvisable it may be given intravenously in 10 to 50 per cent. solution, the need of the body for fluids being the determining factor in the size of the solution. It may be given by hypodermoclysis 2 or 3 per cent. solution (this strength will cause no sloughing), or it may be administered rectally. This is the most unsatisfactory method because of the impossibility of determining the amount absorbed. The postoperative treatment, of course, may be varied, depending on the laboratory findings. Blood-sugar and plasma  $\text{CO}_2$  determination should be made four to six hours postoperatively.

In emergency operations with glycosuria and hyperglycemia the safest procedure is to administer two hours preoperatively 30 to 50 gm. of glucose and 10 to 15 units of insulin. Blood-sugar and  $\text{CO}_2$  determinations should be made immediately postoperatively, and the further treatment be guided by these findings.

In cases in which acidosis is a complication, the diet should contain less protein and, of course, a much decreased fat content with the carbohydrate portion increased. Should this fail to

control the ketonemia, insulin and glucose should be administered. Once the patient is free from the acidotic condition the diet should be gradually increased until it simulates that of the non-acidotic diabetic mentioned above. Surgery should be delayed if possible until the acidosis is cleared up.

In diabetics who are underweight and dehydrated the administration of a large amount of fluid is of great importance, as is the giving of a higher caloric diet than that mentioned above. These patients should have 2500 to 3500 c.c. of fluid a day.

The question of anesthesia should be given great consideration. Local anesthesia is the anesthesia of choice, although gas and oxygen or spinal anesthesia may be used usually with impunity. Ether is somewhat dangerous because of its tendency to produce acidosis, although it may be used in selected cases if careful laboratory examinations are made.

The case which I am presenting today is illustrative of the possibility of doing operations of election in diabetics.

Patient, T. C., age thirty-four years, was admitted to Men's Medical Ward for standardization for diabetes, which from his history he had had for about one year. He had taken insulin on the outside rather irregularly and was on a qualitatively restricted diet. In the routine examination it was found that the patient had a left inguinal hernia, and it was decided to operate on this after the diabetes was controlled. After a period of ten days on a rather high diet consisting of 80 gm. of carbohydrate, 70 of protein, and 160 of fat, making a total of 2040 calories, the patient was standardized and required 5 units of insulin a day to handle this diet.

The operation was performed by Dr. Speese on the left inguinal hernia, from which the patient made an uneventful surgical convalescence. Post-operatively, the patient was given 80 gm. of carbohydrate in each twenty-four-hour period. Feedings were given every four hours until the patient got back again on his normal diet. For a few days he required 10 units of insulin, but we were soon able to cut this down, and the patient was discharged on a maintenance diet which we had taught him to weigh while in the hospital. His urine was negative and his blood-sugar normal.





# CLINIC OF DR. JOHN H. ARNETT

## EPISCOPAL HOSPITAL

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### EPILEPTIFORM CONVULSIONS IN ALCOHOLIC INTOXICATION

**Historical.**—In 1813 Sutton<sup>1</sup> described the occurrence of epileptiform convulsions in an intoxicated individual. Such convulsions, referred to by some writers as "alcoholic epilepsy" and by the laity as "whisky fits," have been recognized by Huss<sup>2</sup> and other writers since his time as being associated with both acute and chronic alcoholism. Convulsions are especially commonly met with in countries where absinthe is taken, due to the convulsive action of the oil of wormwood contained in absinthe. In England and America, however, convulsions due to this cause are of rare occurrence, and I shall omit further consideration of this topic from our present discussion.

Of 88,271 admissions to the Episcopal Hospital during the years 1911 to 1927 inclusive, 614 cases were admitted to the medical and neurologic services or receiving ward with a primary diagnosis of alcoholism. Of this number 18 (2.9 per cent. of alcoholics admitted) had convulsions either immediately prior to or during their stay in the hospital. This figure may be compared to 27 (4.4 per cent.) with delirium tremens and 6 (1 per cent.) with alcoholic hallucinosis.

Of those with convulsions the ages ranged from thirty-four to sixty, half of them being in their fifties. They were of various races and occupations; all were white and all but one were males. The number of convulsions varied from one to many. In the first sample of urine examined the majority had albumin and casts, but these abnormalities later disappeared in most of the cases where further urinalyses were made. In 3 cases where

blood-urea-nitrogen determinations were made, the figures obtained were 12, 12.6, and 23.8 mg. per 100 c.c. of blood. Lumbar puncture findings were recorded in 5 cases, and of these the cells per cubic millimeter numbered 81, 25, 10, 4, and 0. The cerebrospinal fluid was noted as under 18 mm. Hg. of pressure in one case, 12 mm. Hg. in another, and "greatly increased rate of flow" in a third, the spinal fluid Wassermann and colloidal gold reactions being negative. The average number of days spent in the hospital was six, the longest stay was thirty days, the shortest was several hours. No deaths occurred; the condition on discharge being recorded as "good" in 13, "fair" in 4, and "poor" in one who left against advice. In addition to convulsions in 2 (11 per cent.) of the group, the diagnosis of delirium tremens was made and 4 others (22 per cent.) were diagnosed as alcoholic hallucinosis. Our experience here is at variance with the usually accepted teaching that alcoholic convulsions usually appear as a complication of delirium tremens.

**Case Report.**—The woman whom you see lying in a state of stupor interrupted by occasional unilateral convulsions is fifty-two years of age and was admitted to medical service "B" yesterday. She had a history of having been a heavy drinker for many years. In spite of this, except for attacks of headache and vertigo, her health was always good until ten years ago, at which time she had a "stroke" which paralyzed the entire right side of the body and affected her speech. She gradually improved so that after eight weeks she was able to be up and about, but she did not recover full strength on the paralyzed side of her body and noticed, when fatigued, that the right foot had a tendency to drag a little. No complaints referable to her heart, lungs, or kidneys could be elicited, but the attacks of vertigo and headache became so severe that she entered this hospital in 1923. Her clinical record at that time showed the blood-pressure to be 175/105, the Wassermann negative, the urine to have a specific gravity of 1.010, a trace of albumin, and occasional hyaline and granular casts. The positive physical findings noted were moderate sclerosis of the radial arteries, ankle, and patellar clonus on the right side, and a dusky appearance of the optic disk. She was discharged and her condition remained unchanged until about two years ago, when she had an attack of convulsions about which little information could be elicited except that the movements may have been limited to the right side of the body and that the convulsions lasted about one day. She made an uneventful recovery from this attack and resumed her customary habits of living until December 20, 1927, when, after drinking more whisky than usual and while playing cards, she was suddenly seen to become tense and to stare at the ceiling apparently unable to speak or move. After some minutes she

recovered consciousness and was put to bed. On the following morning she began to have convulsions and had already had seven when she reached the hospital.

*Examination* reveals a somewhat obese white female in a deep state of coma which is interrupted at intervals by convulsions, during which, as you see, she grinds her teeth, turns the head and eyes to the right, while the left side of the face, left arm, and left leg undergo continuous clonic convulsive movements, the rest of the body including the abdominal muscles being held in a state of rigidity. These attacks last from one-half to two minutes, and eighteen have been recorded in the space of one and a half hours. After each convulsion the patellar biceps and triceps reflexes are absent for a few minutes, and then gradually return. Between convulsions the left arm and left leg are flaccid, while the right arm and right leg are spastic. The right foot gives a questionable Babinski sign. The blood-pressure is 150/90; otherwise nothing worthy of note is found on physical examination. The temperature on admission was 101° F. by axilla, and today is 104° F. Her leukocytes number 14,000, of which 90 per cent. are polymorphonuclear cells. The fasting sugar, urea nitrogen, and uric acid of the blood are 134, 23.8, and 5.7 mg. per 100 c.c. respectively. The urine has a specific gravity of 1.015, contains a light cloud of albumin, and a few hyaline and light granular casts, but is otherwise negative. The report on the spinal fluid shows that it came out under 12 mm. Hg. pressure, contained 4 cells per cubic millimeter, did not reduce Benedict's solution, was normal as regards globulin content, and gave a negative Wassermann and colloidal gold reaction. The Wassermann reaction of the blood is also negative. An x-ray of the skull is negative for fracture.

**Discussion.**—Whether the story of a previous attack of unilateral convulsions involving the opposite side of the body from the present attack is to be believed is open to doubt. The nature of the "paralytic attack" which occurred ten years ago involving the right side of the body is also open to question. In view of the history of chronic alcoholism with unusual over-indulgence for the past few days alcoholic convulsions would appear to be a plausible diagnosis, although unilateral convulsions due to this cause are somewhat unusual. Jacksonian epilepsy due to subdural hemorrhage or cerebral neoplasm must, of course, be borne in mind as an alternative diagnosis.\* Even if the history of this case were not known, the fact that an individual between the ages of thirty-five and fifty-five begins to have

\* The later history of this case (cessation of convulsions and return to consciousness on the second day after admission with disappearance of all abnormal physical signs and rapid and complete recovery) bears out the diagnosis of alcoholic convulsions.

convulsions should make us suspect alcoholism, especially if syphilis can be ruled out, as is the case here. Alcoholism and syphilis are the two most common causes for convulsions appearing in middle life.

The presence of fever by no means speaks against the diagnosis of alcoholic convulsions. The Episcopal Hospital records of 435 cases of alcoholism in which temperatures were recorded show that 92 (21.1 per cent.) had temperatures over 99.6° F., the highest being 104.2° F. In the great majority of these cases no complications were noted. The presence of a leukocytosis likewise cannot be regarded as evidence against an alcoholic etiology in this case. Of 104 cases of alcoholism whose records contain a leukocyte count, 27 (26 per cent.) exhibited leukocytoses ranging from 11,000 to 23,600. Leukocytosis and fever did not appear to be correlated either with each other or with the presence of gastritis, bronchitis, or infection elsewhere. They were, however, more common in the cases with convulsions than where uncomplicated alcoholism occurred: of 8 cases with convulsions in which leukocyte counts were recorded 5 (62.5 per cent.) exhibited leukocytoses of 11,000 or over, and of 15 in which the temperature was recorded, 12 (80 per cent.) had fever of 99.6° F. or over. These figures, you will perceive, are more than double those for the alcoholic group as a whole. In this connection it is of interest to note that leukocytosis and fever may also be present in idiopathic epilepsy.<sup>3</sup>

Epileptiform seizures occurring during alcoholic intoxication are regarded by some writers as due to epilepsy which has remained latent until unmasked by the effects of alcohol. Dandy and Elman<sup>4</sup> have succeeded in producing a somewhat analogous condition in experimental animals by unilateral injury to the motor cortex. After a lapse of time sufficient for fibrous tissue formation they were able to produce unilateral convulsions, corresponding in location to the damaged cortical area, by the administration of absinthe in dosage far below that required to produce convulsions in normal animals.

Another theory which might explain the convulsions seen in alcoholics is suggested by MacNider's<sup>5</sup> observations upon natu-

rally nephropathic dogs. He found that the administration of alcohol to such animals resulted in a marked increase in the albumin and casts of the urine, a diminution in the excretion of phenolsulphonephthalein, an increase in the blood-urea nitrogen, and sometimes a temporary anuria. It is conceivable, therefore, that a person with diminished renal function might be thrown into a state of uremia through the agency of alcohol with resultant uremic convulsions. The case before you was known to have had hypertension and nephritis four years before her present admission. The present urine and blood studies do not, however, warrant the diagnosis of uremia. The urines of this patient and three others suffering from alcoholism with convulsions have been examined since their discharge from the hospital. The results did not indicate the presence of nephritis.

There is yet a third hypothesis to explain alcoholic convulsions—it is suggested by the experiments of Elsberg and Pike.<sup>6</sup> They found that in cats to whom small doses of absinthe had been administered an elevation of the intracerebral pressure (which they produced by the intravenous administration of *hypotonic* solutions) was accompanied by convulsions. On the other hand, to produce convulsions in animals—to whom *hypertonic* solutions had been administered with a resultant *diminution* of the intracerebral pressure—doses of absinthe in excess of those producing convulsions in normal animals had to be administered.

**Treatment.**—Whatever may ultimately prove to be the mechanism producing alcoholic convulsions it would appear that they are most effectively treated by measures which are directed to dehydration and the lessening of intracerebral pressure. Frequent lumbar punctures, sharp restriction of fluids, saline cathartics by mouth, and 50 per cent. glucose solution intravenously are the methods employed.

**Prognosis.**—The prognosis in alcoholic convulsions in our experience is by no means as bad as has been generally believed. Out of 18 cases so diagnosed in this hospital in the past seventeen years none have died, and the majority were discharged in good condition in less than a week after their admission.

**Summary.**—1. Alcoholic convulsions may occur in cases of either chronic or acute alcoholism.

2. In any case where the cause of convulsions appearing in middle life is being sought, alcohol should be considered.

3. Leukocytosis and fever often accompany alcoholic intoxication, but are respectively about two and one-half and four times as common in alcoholic convulsions as in alcoholism without convulsions.

4. Contrary to what is usually taught, delirium tremens was absent in the majority of our cases of alcoholic convulsions, and recovery was generally rapid, not a single death from this cause occurring in the group studied.

5. Increased intracerebral pressure appears to be a factor in the production of these convulsive seizures, and measures directed toward lessening such pressure are recommended.

6. Unilateral convulsions due to alcoholism may occur. A case so diagnosed is presented.

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# CLINIC OF DR. TRUMAN G. SCHNABEL

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### CLINICAL EVIDENCE JUSTIFYING A CARDIAC DIAGNOSIS

ANALYSIS of the mistakes made in the field of cardiac diagnosis shows quite clearly that such mistakes do not differ in kind or number from those made in other fields of diagnosis. The failure to recognize the presence of cardiac disease constitutes one type of diagnostic error—an error of omission as it were. Under such circumstances the patient's symptoms are usually attributed to dysfunction or pathology of some other organ or system. The mistakes of commission may be of at least two types—those in which heart disease is recognized but the detailed diagnosis is incorrect. It is rather interesting to note in this connection that the clinician seldom fails to appreciate cardiac disease when it actually exists. He may fail to interpret correctly the underlying production mechanism, but, nevertheless, he usually knows that he is dealing with a cardiac disability of some type. The other mistake of commission is made when the heart is credited with disease and no form of check-up will substantiate such an opinion. While all diagnostic errors are unfortunate, it seems especially so when the patient is told that he has heart disease and the evidence actually does not warrant such a diagnosis. Just as soon as a patient is labeled "cardiac" he may become relatively or completely economically insufficient, for the knowledge that he has cardiac disease leaves a profound psychologic impression. Every effort made by succeeding consultants quite frequently fails to erase this impression. Errors in this field of diagnosis may, of course, be a combination of omission and commission.



It would seem to us that all mistakes of cardiac diagnosis would be numerically lessened if the physician always kept clearly in mind the evidence that really points to heart disease. We propose, therefore, this morning to mention some of the facts in the history, the physical findings, and the graphic evidences which usually warrant a cardiovascular diagnosis. When one considers such evidence it becomes apparent at once that some findings are more or less absolute, while others are only supporting in diagnostic strength. It also becomes evident when one attempts to state categorically the evidence constituting good proof for a cardiac diagnosis that the undertaking is difficult, to say nothing of the criticism which such an endeavor will justly call forth. Nevertheless, it would seem of value to state some of the items that suggest in greater or less degree heart disease, if only to remind us that when such items are not available, the likelihood is that the patient is not a cardiac and that the physician must be cautious in making this diagnosis because he may be nullifying an otherwise useful life when he introduces into it the suggestion of heart disease.

The present medical history, past medical history, and social history of a patient would seem to offer no absolute evidence for either an anatomic or physiologic diagnosis. The complaints of dyspnea, cough, edema, weakness, precordial pain, pain down into the arms or up into the neck or jaw, and palpitation are most frequently due to cardiac disability, but they may also have an extracardiac origin. It becomes quite essential, therefore, that the whole historical and symptom picture must be carefully studied so that such other causes may be ruled out. These symptoms either singly or in group usually serve, however, in the rôle of supporting evidence for a cardiac diagnosis. They are also valuable evidence by which an opinion concerning cardiac functional ability can be estimated. Orthopnea means extremely poor cardiac efficiency; while dyspnea at rest, on walking, or after mild exertion will indicate varying degrees of cardiac functional incapacity. Palpitation, precordial pain, and retrosternal or epigastric oppression of varying intensities are also signs of functional incapacity and, therefore, serve as a help

in estimating what the cardiovascular system is able to tolerate. A past medical history of rheumatic fever, chorea, frequent attacks of tonsillitis, and syphilis are most significant etiologic items to consider in cardiac diagnosis. They are important evidence which compel a second thought when other findings are uncertain. Much less importance is to be attached to other diseases including local foci of infection. The social history and family history offer only weakly supporting evidence. Just what rôle hard work and increased alcohol and food consumption play in the production of heart disease is difficult to say. To restate it, then, information gleaned from the patient's history may or may not be important in making a cardiac diagnosis. On the whole the facts developed in the history may be suggestive, not positive, evidence.

The practice of a physician when he carries his findings to the postmortem table is an admirable one indeed, but it also serves a good purpose when the clinician carries his pathology to the bedside. If he will remember what observations the pathologist can make at autopsy, and then will attempt to make the same observations by clinical methods, he will make fewer diagnostic errors and will experience an increasing number of diagnostic confirmations. It may be argued that a postmortem only reveals an advanced situation, but it must be true that antemortem cardiac findings at any time are only a lesser degree of the final picture. The clinician will be able to visualize with a fair degree of accuracy certain gross changes in the heart on the strength of evidences that may be obtained at the bedside or in the laboratory. By the same evidence it can also be expected that he can assume certain microscopic diagnoses. Of course we must presuppose on the part of the examiner an average skill in clinical technic and an average knowledge of medicine. The clinician must then remember that the pathologist at autopsy reports on the size of the heart, whether it is atrophied, hypertrophied or dilated, whether the valves are deformed or have some superimposed lesion, whether there are any congenital, vascular, or muscular lesions, whether there is an unusual amount or a pericardial fluid of unusual character or whether the pericardium is

abnormal. The aorta standing in close relationship to the heart both anatomically and physiologically is also open to pathologic inspection and mensuration.

If then the clinician by palpation, percussion, or x-ray evidence finds a cardiac area of dullness, or a transverse cardiac shadow out of proportion to the expected size, he is justified in almost all cases to conclude that he has found absolute evidence for a cardiac diagnosis including pericardial effusion. The greatest transverse cardiac percussion area or x-ray shadow should normally, we believe for practical purposes, be about 50 per cent. or less of the transverse bony diameter of the chest. There has been a great amount of effort made to establish the normal cardiac x-ray size in any given individual. All of the statistical studies indicate that the greatest transverse diameter of the heart or, as some workers have suggested, the area of the cardiac silhouette bears a relationship to many variable factors. The weight, height, age, sex, and body surface share in this relationship. The clinical application of these more complex methods of study still remains somewhat unsatisfactory for general use. There is no doubt, however, that in the near future tables will be formulated for the clinician, much as they have been in the metabolism field, whereby it can be said with reasonable certainty that a heart is or is not too large or too small. This will be a very desirable achievement when it is remembered how difficult it is at times to determine the size of the cardiac area on physical examination and then reach conclusions as to its normality. If the cardiac impulse is palpable then, of course, the difficulty is not so great, always bearing in mind that the heart may be pushed or pulled out of position. Without a definite knowledge of the position of the cardiac impulse, percussion methods are notoriously uncertain even in the hands of those with average skill. That the cardiac size is of great importance in cardiac diagnosis is manifest when one reads Cabot's book, "Facts on the Heart." This author concludes as a result of his study of 1906 autopsied cardiovascular patients that 77 per cent. of cardiac disease is accompanied by hypertrophy or dilatation of the heart without valve lesions. If one adds to this group

cardiac patients with valve lesions and probably hypertrophy and dilatation as well, the percentage of cardiac cases with large hearts would certainly reach 85 or 90 per cent. It then becomes evident that reasonable absolute evidence of cardiac disease is produced when variation from the normal size of the heart is demonstrable either by x-ray or physical examination. It is in the lesser variations from the normal that the clinician will have some difficulty.

When a competent x-ray examination reveals certain deviations from the normal contour of the heart silhouette, one has almost absolute evidence for cardiac disease, if not absolute then strong supporting evidence. Unusual prominence of the left auricular curve, the pulmonary curve, and a certain increase in the size and shape of the aortic shadow, for example, are very suggestive, especially so when fluoroscopic study reveals unusual pulsations in these areas. The left and right ventricular curves may also be changed from the normal so as to constitute good supporting evidence for a positive cardiac diagnosis.

Evidence for deformed valves with or without superimposed lesions is usually manifested by diastolic or systolic murmurs with thrills. The murmur and thrill in themselves only indicate that there is some obstruction or regurgitation of the blood-stream flow through a valve orifice, but it can be assumed that such events are due to a crippled or diseased valve or perhaps a relatively wide valve orifice due in any event to cardiac pathology. The diastolic murmur with a thrill or even without a thrill constitutes an almost absolute finding for a cardiac diagnosis, especially so when supported by other evidence of cardiac pathology. The possibility of a functional diastolic murmur must be conceded, but such instances must be very rare. Systolic murmurs are weaker links in the chain of evidence for cardiac disease except when accompanied by thrills or other evidences of heart trouble such as an increased area of cardiac dulness and diastolic murmurs. The findings of a to-and-fro friction murmur accompanied by a friction fremitus is also an absolute criterion for a pericardial diagnosis. It must, however, be remembered in this connection that endocardial murmurs

may simulate those of pericardial origin. The typical water-bottle type of x-ray shadow constitutes absolute evidence for pericardial effusion, but may not necessarily be present. Sometimes a diagnostic puncture may yield positive evidence for a pericardial effusion, and the characteristic water-bottle shadow may not be evident. A positive pericardial paracentesis constitutes absolute evidence for a cardiac diagnosis.

Congenital cardiac lesions in the main have the same absolute and supporting evidence to indicate a cardiac diagnosis, namely, some local or general variation in the contour of the cardiac silhouette, systolic and diastolic murmurs and thrills, and on occasions continuous murmurs. The murmurs usually indicate valvular difficulties on the right side of the heart rather than the left and there is in the past history little evidence for a postnatal etiologic factor. Supporting criteria, such as clubbed fingers, cyanosis, past or present, and unusual fluoroscopic pulsations, make for a more certain diagnosis. The diagnosis of thyrocardiac disease, angina pectoris, and cardiac infarction must rest largely on supporting evidence, although in the main the diagnostic evidence differs little from the findings in cardiac disease generally.

Variations from the normal cardiac rhythm offer valuable evidence in the field of cardiac diagnosis. Such arrhythmias justify a physiologic diagnosis at least, and by inference an anatomic one may frequently be assumed. As a rule when such an assumption is warranted the pathologic lesion writes its own record. If cardiac auscultation, palpation of the radial pulse, and electrocardiographic, polygraphic, or sphygmographic findings reveal auricular fibrillation or flutter, heart-block, and pulsus alternans, the clinician has absolute evidence for a cardiac diagnosis. As time goes on other cardinal arrhythmias are taking on an ever-increasing rôle in cardiac diagnosis with the exception of the so-called respiratory or juvenile arrhythmia. Transient arrhythmias may, of course, have an extracardiac excitation focus, but it must be shown whether or not a normal heart will respond in an abnormal way to such stimuli. It has been thought by some that premature contraction arrhythmias and paroxysmal

tachycardia may exist without real heart disease. As has been intimated, such arrhythmias are being regarded with more and more serious significance as time goes on. Certain observations only made possible by electrocardiographic study constitute absolute evidence of cardiac disease. Tracings which fulfil the stated criteria for conduction difficulties in the auricles, ventricles, or indeed in any other portion of the conduction system, are almost certain evidence for disease. Electrocardiographs which are of unusually low amplitude and have inverted T waves in Leads I and II taken in patients not under digitalis therapy are immediate evidence for cardiac disease. There are, of course, other variations from the normal electrocardiographic curve which serve as important supporting evidence.

The relationship of arterial-tension changes to cardiac disease has not been clearly defined, but it does seem that with a more or less prolonged period of hypertension cardiac changes will follow. In the main it can be stated that blood-pressure readings are merely suggestive of possible cardiac disease when they vary from the normal, and this applies also to pulse-pressure observations. The quality of the radial pulse as well as its rate and rhythm are only contributory evidence in the diagnosis of cardiac disease. The water-hammer pulse and signs that go with it—pulsus paradoxus and other types of pulses—usually occur as a result of cardiac lesions, but may be present in extracardiac conditions.

An important objective in cardiac diagnosis is an estimate of the functional capacity of the heart. Unfortunately at the present time it would seem that the determination of cardiac capacity must be based largely upon the degree of symptomatology. Under such circumstances the judgment of different individuals, irrespective of previous experience, will show a considerable variation. If an agreement might be reached whereby certain symptoms of certain degree could be labeled a deficiency of such and such an amount, all cardiac diagnoses would be considerably easier. Obviously this cannot be expected. Many exercise-tolerance tests for the determination of cardiac efficiency have been suggested from various sources.

There seem to be objections to all of these methods and none have met with universal approval. It develops that each examiner has some pet scheme of arriving at his conclusions. Some make observations on the pulse-rate or blood-pressure before and after exercise for variable periods of time. As examiners work along they seem to attempt fewer and fewer observations of this kind, and in their suspected cardiac depend more or less on appearances suggesting distress, dyspnea, and cyanosis when a certain type of exercise is carried out. Exercise tolerance in an individual is dependent upon many factors, so that in themselves such tests cannot be expected to offer very certain evidence for cardiac disease. For example, the bank clerk leading a very sedentary life may tolerate exercise very poorly and exhibit easy dyspnea after exertion, but very obviously he may have a sufficient cardiovascular apparatus if he is permitted to train himself up gradually to a higher level of endurance. The victim of tuberculosis or pernicious anemia, the neurocirculatory asthenic, and other diseased individuals will also present signs of distress after exertion with what is apparently a normal heart. Nevertheless, poor exercise-tolerance tests are supporting strength for other observations in the field of cardiac diagnosis. If cardiac disease is well advanced, cardiac functional disability writes very clearly on the page of symptoms. If, however, there seems to be no evidence for certain anatomic alterations, the determination of cardiac efficiency or lack of it may be very difficult to decide. Under such circumstances cardiac diagnosis rests or falls on the physiologic opinion. The clinician should be very slow in making his diagnosis if he has no evidence for anatomic difficulty in the background. On the other hand, it must be also remembered that anatomic changes are not incompatible with cardiac sufficiency, but this is very seldom true. If possible every cardiac diagnosis should indicate pathological, anatomic, and physiologic variations from the normal. Included in the latter should be an approximate estimate of cardiac efficiency in terms of everyday physical tolerance.

It would seem then that, in the main, the clinician is justified

in making a cardiac diagnosis when he discovers in his patients certain evidences for variation from the normal anatomy of the heart, and certain variations from the normal rhythm. Chief among anatomic variations is a heart that is without the normally expected size. Next in importance are diastolic murmurs. Systolic murmurs should not arrest the clinician's attention unless they have some unusual quality, and more important than this when they are accompanied by a thrill. We have intentionally omitted any reference to the character of sounds and the force of the cardiac impulse. The cardiac sounds are capable of such a varied interpretation on the part of the clinician that it would be unsafe to place very much reliance on such observations. The reduplication and accentuation of second sounds and the character and intensity of the first sounds at the different valve areas are of considerable supporting strength, but the examiner always must bear in mind that he should have other more positive evidence for cardiac disease before he takes such a stand. Permanent arrhythmias are also very certain evidence for heart disease with the exception of the juvenile or respiratory type. Transient arrhythmias must also be regarded as very nearly certain evidence. Most of the other symptoms and findings generally discussed in cardiac diagnosis must in themselves be considered with some degree of caution before they are allowed to sentence an individual to the life of a cardiac.

The discussion this morning may seem to be exceedingly elemental, but it concerns basic considerations which must be continually remembered if we wish to deal fairly with our patients. A study of patient records shows an appreciable percentage of instances in which a cardiac diagnosis is made with no reasonable evidence to justify the procedure. The big objective we have had in mind this morning is to impress upon you the gravity of making a positive cardiac diagnosis when there actually is no real evidence at hand. Further than this, that there are comparatively few ascertainable facts which in themselves allow the clinician to place his patient in a cardiac category, but that there are many findings which constitute only



supporting testimony in the field of cardiac diagnosis. At times a sufficient number of lesser evidences may be assembled to establish a positive diagnosis with no major finding. Generally, a reasonably absolute criterion should be demonstrable in our patients before the heart is suggested to our patients. As in all other fields of medicine we must study our patients completely both from the physical and psychical standpoint and then weigh all of the evidence in the balance. An abnormal size of the heart, evidence for cardiac blood flow disturbances, and the pathologic disturbances of cardiac rhythm are nearly always necessary before one is justified in saying, "you have heart trouble."

# CLINIC OF DRS. LEWIS H. HITZROT AND KATHERINE S. ANDREWS

FROM THE GASTRO-INTESTINAL CLINIC OF THE UNIVERSITY HOSPITAL

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## THE VALUE AND PRACTICABILITY OF DUODENAL DRAINAGE IN THE STUDY OF GALL-BLADDER DIS- EASE IN AN OUT-PATIENT CLINIC

DRAINAGE of the biliary tract through the duodenal tube has had innumerable trials since Lyon, in 1919, first advocated it. Recent medical literature contains an enormous amount of evidence both for and against the procedure, and leaves one in doubt as to its value. This uncertainty is based largely upon the questions as to whether bile from the gall-bladder can be obtained at will through the tube, and whether the study of bile so obtained is of any clinical value. Furthermore, if the satisfactory results obtained in an elaborately equipped office or hospital be granted, there is no wide-spread evidence that the profession considers the measure feasible in an out-patient clinic or an ordinary private office.

It is not our intention to enter into the controversy as to whether or not bile obtained by placing a tube in the duodenum and injecting various stimulating substances is bile from the gall-bladder. The work of Lyon, Boyden, and Whitaker and the recent contribution of Lake<sup>1</sup> encourage us to believe that gall-bladder bile can be so obtained. Assuming this to be true, our study is concerned with the other questions, namely, the clinical value of the study of bile so obtained and the practicability of such study under ordinary circumstances. It is in respect to these two questions that the following cases and brief study are reported.

<sup>1</sup> Lake, M.: Observations on the Origin of "B" Bile Obtained by Lyon's Method of Biliary Drainage, Amer. Jour. Med. Sci., 174, 786-793, December, 1927.

We began then with the assumption of the following general facts which we feel to be reasonably well proved:

First, that the gall-bladder can be emptied into the duodenum, at least partially, while the tube is in place.

Secondly, that certain substances instilled into the duodenum or taken by mouth will cause an increased flow of bile, of which a part has the characteristics of gall-bladder bile.

Thirdly, that magnesium sulphate in proper amount and strength, presumably by relaxing the duodenal wall or sphincter of Oddi, or both, will release stored bile effectively and will not interfere with microscopic study of the centrifuged bile sediment.

The organization of a gastro-intestinal clinic at the University Hospital in the fall of 1926 offered opportunity to study a consecutive series of gall-bladder suspects according to the method described below. One or more successful drainages were obtained in 41 patients. Coincidentally, 10 private cases and a series of 39 ward patients were studied in the same manner, partly to increase the total of material and thus aid judgment of results and partly for comparison. This made a total study of 90 cases. The criteria on which a diagnosis of pathology of the biliary tract was made were the presence in a fresh centrifuged sediment of: (1) Clumps of calcium bilirubinate; (2) cholesterin crystals, and (3) large numbers or clumps of bile-stained pus or epithelial cells. Mucous flecks or plugs found occasionally, when weighed with other evidence, were sometimes suggestive of pathologic change. The technic used was in general that described by Chester M. Jones,<sup>1</sup> and was as follows:

**Technic.**—The tube was introduced at the beginning of a two-hour period when the patient was in the fasting state, and the bulb entered the duodenum, with rare exceptions, within a half-hour. Although the fluoroscope was used in several of the ward patients to verify the position of the bulb, in the clinic the spontaneous flow of viscid bile was considered satisfactory evidence that the bulb had passed the pylorus. A few swallows of water or 1/150 gr. of atropin sulphate by hypodermic were

<sup>1</sup> Jones, C. M.: The Rational Use of Duodenal Drainage, *Arch. Int. Med.*, 34, 60-78, 1924.

occasionally used to hasten the process. Two specimens of bile were collected—one before, the other thirty to sixty minutes after the injection of 50 c.c. of 33 per cent. solution of magnesium sulphate. Ten c.c. portions of each of these were promptly centrifuged at high speed and the sediment examined under the microscope.

Two points of this technic should be emphasized: First, the relative ease with which bile may be obtained, and second, the importance of microscopic study of a fresh sediment which has been obtained by high-speed centrifuging.

The following cases, chosen from among the 90 studied, are presented in order to show concretely the manner in which we have found duodenal drainage to be both useful and practicable.

Case I.—E. McM., an Irish woman of sixty-one years, was first admitted to the clinic August 22, 1927. Her chief complaint was an intense, generalized itching which began ten weeks before admission. This was accompanied by marked nervousness and intermittent attacks of moderately severe epigastric pain which sometimes radiated to the back. Nausea and vomiting were not present. Constipation had always been marked.

The chief points of interest in the past history were an attack of typhoid fever "years ago," and the removal of a "cyst" from the breast three years before—exact nature of lesion unknown. Family and social history were negative.

On physical examination the important findings were a slight but definite jaundice of skin and sclerae and a questionable mass just to the right of the midline and above the umbilicus.

A Van den Bergh test was reported as direct, negative; indirect 1.2 units. A Graham test was reported as showing a normal gall-bladder. Blood-count and urinalysis were also normal. A gastric analysis showed no free hydrochloric acid in any specimen, and a highest total acidity of 26. Study of pancreatic ferments showed an abundance of enzymes present. Attention was next turned to the biliary tract. The duodenum was entered with difficulty in this case, but several satisfactory drainages were finally achieved. In all of these the sediment studies showed great quantities of pus-cells, clumped and singly; but no cholesterol or calcium bilirubinate. A tentative diagnosis of cholangitis with partial blocking of the ducts was made on the basis of these reports and the patient treated accordingly, *i. e.*, medically. By the middle of June, 1928 the itching had entirely disappeared, the Van den Bergh test was reported as indirect 0.9, the patient was gaining in weight and was in good health.

The first suspicion in this case was that of carcinoma of the pancreas. This diagnosis was suggested by the rather slow on-

coming jaundice with pruritus, the negative cholecystogram, and the achlorhydria. The presence of plenty of pancreatic ferments did not confirm this theory however. Further investigation by means of the duodenal tube revealed so many pus-cells in all specimens that it seemed reasonably certain that the pathology lay in the biliary tract. A diagnosis of cholangitis was accordingly made, and subsequent events seemed to prove this diagnosis correct.

**Case II.**—I. R., a white man of forty years, Russian Jew by birth, came to the clinic April 18, 1927, complaining of attacks of epigastric pain which first developed six months previously. For the most part the pain was dull and aching and intermittent, but at times it became severe and then radiated to the right costal and interscapular regions. Attacks came on about two hours after meals, and were made worse by food. Nausea, vomiting, and jaundice were not present. Bowels were regular until onset, but since then had become markedly constipated. There was considerable distress from abdominal distention. Patient stated that ten days before admission he passed a dark, tarry stool. In spite of a good appetite there was a loss of 20 pounds of weight in six months.

The past medical, family, and social histories were essentially negative.

The chief features on physical examination, aside from some bad teeth and diseased tonsils, were a palpable liver edge with slight tenderness over this, and some tenderness in the epigastric region.

Blood-counts, urinalyses, feces examination, and Wassermann reaction were negative. Three gastric analyses, one done after histamin injection, showed no free hydrochloric acid in any specimen, and low total figures. A gastro-intestinal roentgenologic study was negative, except for hyperperistalsis with almost complete segmenting of the stomach. A cholecystogram was reported as showing no evidence of concentration and being otherwise normal, a "borderline gall-bladder."

A duodenal drainage was done. This showed much calcium bilirubinate and great numbers of bile-stained pus-cells. A diagnosis of cholecystitis was then made, and the patient sent into the ward for surgery. At operation a much thickened gall-bladder was found—tense and enlarged. There were no stones anywhere, and a thorough exploration of the stomach, pylorus, and duodenum disclosed no other pathology. A cholecystectomy was done June 6, 1927, and the patient soon after returned to his work in good health.

The relatively short history of this case, the statement of tarry stool with rather sudden onset of marked constipation, the loss of weight, the achlorhydria persisting even after the injection of histamin, raised the question of early malignancy in this patient. On the other hand, the nature and location of the pain and ten-

derness together with the roentgenologic studies suggested gall-bladder disease. Study of the duodenal sediment which showed much calcium bilirubinate and many pus-cells confirmed the suspicion of gall-bladder disease. A diagnosis of cholecystitis was made, therefore, and this was proved at operation to be the correct one.

Case III.—M. V., a Porto Rican woman of twenty-eight years, came to the clinic on May 5, 1927. Her story was that since the birth of a child eight years before she had suffered from attacks of "indigestion" which consisted of sour eructations with some nausea and occasional vomiting. About eight months previous to admission, however, the nature of the attacks changed. The pain was now localized not so much in the epigastrium as in the right hypochondrium, and was so severe as to require the use of morphin for relief. In addition to the attacks of severe pain she suffered from an almost constant dull ache in the right hypochondrium which radiated to the right shoulder region. The pain bore no relation to food in either time or quality, and was not associated with nausea and vomiting as a rule. Moderate constipation was present. On one or two occasions there was definite jaundice following the attacks of pain. The rest of the history was essentially negative.

Physical examination revealed only the faintest suggestion of icterus in the scleræ, but there was definite tenderness below the right costal margin. Examination was otherwise negative.

Gastric analysis was normal. A blood-count and a urinalysis were also normal. A cholecystogram was done, but reported as "unsatisfactory." A duodenal drainage showed many cholesterol crystals, some calcium bilirubinate, and a considerable number of bile-stained white blood-cells and epithelial cells.

This drainage confirmed the clinical diagnosis of cholelithiasis, and in spite of the absence of roentgenologic evidence the patient was operated upon. Two large faceted stones were removed by the surgeon, and the patient made an uneventful recovery.

In these cases, representing cholangitis, cholecystitis, and cholelithiasis, we feel that one must concede the value of duodenal drainage studies. The first 2 were chosen to illustrate how drainage may be useful in cases with rather atypical stories of biliary tract disease; the third, to show how it may confirm the clinician's position in fairly typical cases when roentgen-ray evidence is lacking. In Case I the clinical data pointed toward malignancy of the pancreas, and roentgen-ray examination of the biliary tract was negative. In Case II the clinical evidence

was conflicting, and the roentgen ray uncertain. In Case III the history and findings were fairly typical, but there was no confirmatory roentgen-ray evidence. By means of sediment studies, however, it was possible to arrive at a correct diagnosis of biliary tract disease in each instance. All 90 cases of this series were studied in the same fashion. The results obtained are given below:

**Results.**—The proportion of abnormal sediments exceeded our expectation even for a series of suspects. Of the clinic series, 60 per cent. were positive; of the ward-group, 51 per cent. Successful cholecystograms, either by oral or intravenous method, were obtained in 67 (74 per cent.) of the 90 cases. Difficulties not easily overcome accounted for the 23 failures, most of which occurred in the dispensary group. In 41 (61 per cent.) of these 67 cases the x-ray reported diseased gall-bladder, 9 were doubtful, 13 negative, and 4 unsatisfactory in examination. Duodenal drainage was confirmatory of clinical and roentgenologic findings in 39 (58 per cent.) of these cases.

Twenty-six (28 per cent.) of the entire 90 were operated upon. Twenty-two of these showed diseased gall-bladders, 2 were reported as having only adhesions, and 2 were declared normal. In 5 instances where subsequent clinical findings were definite the drainage proved misleading. Roentgen-ray and clinical evidence were doubtful or contradictory in 27 cases (30 per cent.). Of these, the sediment findings were pathologic in 16 cases (60 per cent.). Ten of these 16 patients refused or postponed operation, but of the 6 operated upon all had disease of the biliary system. In 30 instances (33 per cent.) no excess of pus, epithelium, or crystals could be obtained. From this the biliary tract was reported, therefore, as "probably not diseased." Finally, 8 individuals (10 per cent.) not suspected of biliary disease were included as controls. No one of these showed more than an occasional pus-cell in the duodenal sediment.

**Discussion.**—Jones' method suggested the feasibility of studying out-patient cases and, although our technic was in some respects less accurate, his findings were confirmed. A variety of substances were tried to stimulate the flow of bile;

egg-yolk and cream, shown by Boyden and others to bring on contraction of the gall-bladder, were not feasible because they obscured the microscopic picture when returned with bile. Other fatty substances, as oleic acid and olive oil, were given up in turn as holding no advantage over the well-tried magnesium sulphate. Constant observation of the flow of bile we found not practicable generally, although such observation may be valuable. Nor were bacteriologic studies made, proof of their small value being conceded. Examinations of the first specimens collected, presumably liver bile, were thought to be not necessary, but were done for comparison so as to judge more accurately the origin of the elements found in the second portion.

Any diagnostic measure in gall-bladder study nowadays should be compared with the Graham-Cole cholecystogram. While this evidence is of the greatest value in reaching a conclusion, the specificity of the test breaks down in two respects. In the first place a relatively large number of "no gall-bladder shadow" reports follow the oral method of administering the dye. Such a report leaves the clinician in doubt as to whether the picture was the result of poor absorption of dye from the bowel, blocking of the channel of entry into the gall-bladder, or to lack of concentrating power. To attempt to single out the actual cause by giving the dye intravenously is next to impossible in an out-patient clinic and not easy in a ward. In the second place a gall-bladder in the early stages of disease, with or without stones, may contract and expel the dye, and yet in spite of a normal picture be much in need of treatment.

There is, then, in spite of excellent co-operation from an x-ray department, usually a certain percentage of failures to get aid from this source (cf. Case III). As noted above, the situation remained in doubt in 27 (30 per cent.) of our series, despite thorough clinical and x-ray study, for one or more of the reasons just given. It was in these doubtful cases that duodenal drainage proved most useful (cf. Cases II and III). In the larger proportion of cases, however, (39 of our series), the clinical impression and the x-ray findings agreed, and sediment studies furnished only confirmatory evidence, such evi-



dence being valuable, however, in making the physician's position more secure.

Of the 7 instances where drainage was misleading, lapses in technic, failure to get gall-bladder bile, or improper interpretation of the sediment picture, probably account for the error. Of the 30 cases which showed negative drainages, one case at operation had a normal gall-bladder, and one other, stones with patent ducts. Frankly, the negative drainages were misleading in both these instances. A single negative sediment examination we feel is of relatively little value in the presence of suggestive findings and should be repeated. If this be done, a certain percentage will confirm the other tests. Several instances of a negative followed by one or more positive tests occurred in the series. In short, positive tests are more reliable than negative ones.

Where no evidence of concentrated bile can be secured in two or more drainages, it is justifiable to diagnose cystic-duct block. Operation confirmed such diagnosis in three instances.

**Comment.**—The study of biliary drainage was begun with frank skepticism that examination of bile by this method would produce diagnostic evidence to justify its use routinely. The outcome of the cases susceptible of proof, however, has led to the belief that many diagnostic problems involving the gall-tract can be solved with the evidence it affords.

Prompt microscopic examination of a well-centrifuged sediment appears the method of choice. Proper interpretation of the microscopic picture requires experience. The whole examination, however, can be done easily by a thoroughly instructed technician.

The results of trials in 41 out-patient and 10 office cases indicate that duodenal drainage can be carried out within the time limit of the dispensary visit. The equipment needed, aside from a good centrifuge, is available in any clinic and in most offices.

**Conclusions.**—1. Examination of the bile sediment for evidence of pathology in suspected biliary tract disease is not an infallible test.

2. Careful comparison, however, in 90 different individuals, with other standard diagnostic measures, leads to the conclusion that such examination has value. It frequently enough completes the chain of evidence for or against a diagnosis of biliary disease to warrant its inclusion among routine diagnostic procedures.

3. It is neither so difficult, time consuming, nor expensive that it cannot be used in out-patient gastro-intestinal clinics or in private offices.

## TABLES

## I.

Diagnostic results in 24 cases proved at operation to have gall-bladder disease.

Diagnostic procedure.	Positive.	Doubtful.	Negative.	Total.
History . . . . .	22	2	0	24
Physical examination . . . . .	21	0	3	24
Drainage . . . . .	20	2	2	24
Roentgen ray . . . . .	12	5	1	18
Drainage and roentgen ray . . . . .	11	7	0	18

## II.

Diagnostic results in 34 cases believed to have gall-bladder disease, but not operatively proved.

Diagnostic procedure.	Positive.	Doubtful.	Negative.	Total.
History . . . . .	32	1	1	34
Physical examination . . . . .	28	4	2	34
Drainage . . . . .	26	4	4	34
Roentgen ray . . . . .	18	2	6	26

## III.

Drainage sediment findings in 90 cases.

Crystals . . . . .	23
Pus . . . . .	20
Pus and crystals . . . . .	9
Negative or inconclusive . . . . .	30
Eight controls (gall-bladder disease not suspected), drainage negative.	



# CLINIC OF DR. EDWARD ROSE

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## CARDIOVASCULAR DISEASE ASSOCIATED WITH NON-TOXIC GOITER

SINCE attention was first called to the association of heart disease with thyroid enlargement by Adelman in 1828 it has been known that various types of cardiovascular derangement may occur in association with hyperthyroid states. The frequency of cardiac disease in hyperthyroidism has been variously estimated at from 20 to 35 per cent., with severe damage in from 2 to 6 per cent. (Thacker<sup>1</sup>). It is only necessary to mention in this connection that varying degrees of cardiac disorder may be found both in the so-called exophthalmic goiter and adenomatous goiter with hyperthyroidism. Such evidence of cardiopathy may vary from occasional runs of extrasystoles or transient auricular fibrillation to the most serious and indeed occasionally fatal forms of congestive heart failure. Both from a diagnostic and therapeutic standpoint recognition of cardiac damage is of vital importance if the present low surgical mortality in the treatment of hyperthyroidism is to be maintained or further reduced.

Despite the recognition of the importance of cardiovascular degeneration in hyperfunctioning or abnormally functioning states of the thyroid, comparatively little attention has been directed toward the phenomenon of cardiovascular disease occurring with simple or non-toxic enlargements of the thyroid gland. It is with this aspect of the question that we wish to deal here. A search of the literature revealed a curious paucity of observation concerning the association of these two conditions. It should be emphasized that striking though this asso-

ciation be, it cannot at present be considered more than an association. No matter what speculation it may lead to (and this will be discussed later), we must be content for the present with pointing out that the two types of disease process exist coincidentally with far greater frequency than has been generally recognized heretofore.

The cases described below were under observation in the University Hospital during the past year. They constitute only a portion of a series of similar but less striking instances observed during the past year in the Thyroid Clinic of this hospital, a description of which is prevented by lack of time and space.

Case I.—L. J., colored woman, aged sixty-two years, married, and the mother of seven children, was admitted to the Surgical Service of Dr. Charles H. Frazier in the University Hospital on December 24, 1927 with a chief complaint of swelling in the neck and difficulty in breathing. An enlargement of the left lobe of the thyroid had been first noticed thirty years before. This had continued to enlarge progressively and later involved the right lobe of the gland. For the past three or four months she had had increasing difficulty in breathing and a dry, non-productive cough. There was a rather vague history of palpitation and occasional non-radiating precordial pain. There had been occasional nausea and vomiting. There was no history of peripheral edema and no significant urinary symptoms. There had been no loss of weight. The past medical history was essentially negative; she had lived in Maryland all her life and had always worked hard. She had 2 sisters who suffered from similar enlargements of the neck.

Examination showed the patient to be orthopneic, but not cyanosed, and exhibiting no edema or jaundice. Blood-pressure was 110/62, pulse 88, temperature 99.2° F., respirations 20. The eyes showed bilateral arcus senilis; the teeth were in bad condition with marked pyorrhea. The thyroid was diffusely enlarged, fairly soft with a cystic consistency and a lobulated character to both lobes. There was no bruit or pulsation, and no distended veins were present superficially. Examination of the lungs showed an occasional dry metallic cough, limited expansion of both sides of the thorax, and findings suggestive of bilateral pleural effusion. The heart was enlarged to percussion, the sounds were of poor quality, and there were occasional extrasystoles. No murmurs were heard. The liver was slightly enlarged and there was rather marked diastasis of the recti and a large umbilical hernia. The urine contained constantly a heavy cloud of albumin and an occasional granular or hyaline cast. Blood-sugar on January 5th was found to be 166 mg. and a sugar tolerance test showed a definite impairment of her ability to metabolize carbohydrates. On January 1, 1928 she was transferred to the Medical Division, where she was placed upon a somewhat restricted

carbohydrate intake. On December 31st bilateral thoracentesis was performed and about 500 c.c. of clear amber fluid removed from each side. Despite the elevated blood-sugar only an occasional trace of sugar appeared in the urine, and there were no ketone bodies or other evidence of acidosis. Thoracentesis on the left side again became necessary on January 14th. By January 16th the patient had become much worse, was unable to breathe except when sitting erect, had a weak pulse and heart sounds that were distant with a faintly slapping quality. An electrocardiogram indicated the presence of severe myocardial disease; the pulse-rate remained slightly elevated, varying from 82 to 110. Despite the evidence of cardiac decompensation basal metabolism was found to be only +10 per cent. on December 26th, and a similar result was obtained when the test was repeated. On January 17th the patient died suddenly. Autopsy was performed four hours after death. A summary of the findings follows:

The thyroid showed an irregular lobulated enlargement, somewhat greater on the left, which consisted of cystic areas scattered about in a diffuse colloid struma such as is characteristically found in the so-called simple colloid goiter. There was a marked overgrowth of stroma and the acini varied tremendously in size. A few small hemorrhagic areas were noted, but the microscopic picture was not that seen in the so-called exophthalmic or toxic adenomatous gland. The heart showed marked enlargement, the external surface of the pericardium was covered by a fibrinous exudate. The endocardium was normal. Throughout the myocardium there were a number of old scars varying in size from minute areas up to larger ones several millimeters in diameter. These areas were of various ages and they consisted of typical granulation tissue with bands of newly formed blood-vessels and phagocytic cells. No definite relation to the coronary system could be made out, although it seemed likely that these scars resulted from circulatory occlusion. The muscle-fibers in general were distinctly enlarged and had prominent blunt-ended nuclei. Around the scars, however, the fibers were very atrophic. Both the bases of the aortic and mitral leaflets showed atheromatous changes. There was moderate atherosclerosis of the aorta, and a section of the dorsalis pedis artery showed marked arteriosclerosis. In addition there was a confluent bronchopneumonia with fibrinopurulent pleurisy on the left and a bilateral hydrothorax.

The revised clinical diagnosis was myocardial disease with arteriosclerosis and decompensation, terminal pericarditis, and beginning purulent pleurisy, diabetes mellitus, and colloid and cystic goiter, non-toxic.

**Case II.**—The patient, Mrs. E. W., a colored woman aged fifty years, was first admitted to the Surgical Service of Dr. Charles H. Frazier on June 30, 1927, with the complaint of enlargement of the neck, nervousness, and loss of weight. She had had a goiter for about twenty-five years, but it had changed little in size and had given her no trouble until about eight months before admission, when she began to notice increasing nervousness, marked fatigability, palpitation, and loss of weight. At this time the neck began to increase in size. She had lost 35 pounds in the eight months before admission. Her history was otherwise of no significance. Examination at that time

showed evidence of loss of weight, marked weakness, a rapid thready pulse, varying in rate from 110 to 130, and a blood-pressure of 140/70. There was no exophthalmos, but her neck showed a marked irregular nodular enlargement of the thyroid, the right lobe being as large as a small orange. Most of the gland was fairly soft, but there were several firm nodular areas in both lobes. The heart sounds were distant and of poor quality, but the rhythm was normal and no murmurs were heard. x-Ray of the chest showed some widening of the aortic arch with no cardiac enlargement. Examination of the blood and urine was essentially negative. The clinical picture and history strongly suggested hyperthyroidism of secondary type—the so-called toxic adenoma; but the basal metabolism was reported as  $-2$  per cent. Despite this finding, a subtotal thyroidectomy was performed on July 5th. Convalescence was uneventful, but the pulse-rate remained rapid throughout, and ten days after operation the basal metabolism was  $-5$  per cent.

The patient was discharged and was examined in the Out-patient Clinic one month after operation. At this time a small recurrent mass was noted in the left lobe of the thyroid. The pulse-rate was still rapid, and the patient complained of some shortness of breath. The mass persisted and on October 5th the patient was readmitted for observation. At this time her basal rate was  $-10$  per cent.; she complained of nervousness, palpitation, and rapid heart action. There was slight swelling of the feet and an occasional dry cough. The basal rate was determined again and this time found to be  $-20$  per cent. She was discharged on October 30th without removal of the recurrent thyroid nodule. She was again admitted November 16th, complaining of an increase in nervousness, marked dyspnea, and further enlargement of the recurrent thyroid mass. Examination at that time showed a blood-pressure of 175/95 with a pulse-rate varying from 74 to 110. There was evidence of moderate vascular sclerosis; cardiac rhythm was regular, but the sounds were weak. No murmurs were heard and no enlargement could be demonstrated. The thyroid nodule was extremely tender. The basal rate at this time was  $-26$  per cent., but following the administration of thyroid substance, rose in five days to  $-13$  per cent. and subsequently was brought up to  $+1$ . Coincidentally, her symptoms decreased and she felt better in general. The blood-pressure remained moderately elevated and a fluid test of kidney function showed some impairment of her ability to concentrate the urine. An electrocardiogram showed a mild grade of heart-block at this time. She was discharged improved January 1st. On January 26th she was examined in the Out-patient Clinic and had a blood-pressure of 160/100 with a pulse ranging from 106 to 118. She still complained of some nervousness, dyspnea, and fatigability. Although she was instructed to return for further observation, she was lost to view.

We have for consideration, then, two patients: one middle-aged, one elderly, both presenting thyroid enlargements which were not associated with those evidences of toxicity which are generally accepted—that is, signs and symptoms of increased metabolic rate. In both instances there was definite evidence of

cardiovascular disease: in the first case associated with decompensatory phenomena, in the second case evinced by a persistent tachycardia, hypertension, arteriosclerosis, mild decompensatory phenomena, and, on one occasion, electrocardiographic findings of a minor grade of heart-block. In neither case was there evidence of tracheal compression by the enlarged thyroid.

References to the association of these conditions in the literature are comparatively few. Coller<sup>2</sup> has discussed this question perhaps more fully than any other American writer and has shown in a study of 300 cases of adenomatous goiter with normal basal rates and over twenty years of age that the incidence of cardiac enlargement, tachycardia, auricular fibrillation and suggestive symptoms, such as palpitation and dyspnea, increased progressively from the third to the sixth decade. He grants that not all the cardiovascular lesions found can be considered due to goiter, but points out that the percentage of incidence is much greater in this group than in ordinary groups in the same decades. He further suggested that these cardiovascular lesions might be due to a low-grade, long-continued toxemia of a nature not recognized as yet. It is, of course, possible that some of the damage might have been done during mild exacerbations of hyperthyroidism which went unnoticed. If such adenomatous glands do produce a secretion directly toxic to the cardiovascular apparatus, but not reflected by an elevated basal rate, it is conceivable—as Coller suggests—that a long-continued bombardment with toxic material might result from different adenomatous areas being in different stages of degeneration at various times.

Among others who have recognized the association of heart disease with simple goiter are Pardee,<sup>3</sup> who in 1925 noted that simple adenomas without increased basal metabolism are associated with a tendency to cardiac abnormalities; Loeper and Mougeot<sup>4</sup> who in 1926 reported three patients with symptoms of decompensation appearing simultaneously with enlargement of the thyroid, and three other cases in which the appearance of the goiter preceded the dilatation of the left heart; and Munly<sup>5</sup> who in a review of the literature on thyroid heart disease men-



tions that non-toxic goiter is potentially dangerous to the myocardium and believes that a large percentage of cases showing persistent enlargement of the gland will eventually show also serious cardiovascular disorders.

German authors have discussed for a number of years the possible nature of different types of thyroid heart disease. Gmelin,<sup>6</sup> who discusses in detail the history of the study of thyroid heart disease, distinguishes between goiter hearts produced by mechanical causes and those produced by toxic agencies. He states that some cases show a combination of the two types. The mechanical type is thought to be due—according to F. Rose, who first clearly recognized the effects of goiter on the heart in 1878—to pressure on the trachea resulting in increased work for the right heart and extension of the right border with slower venous circulation. Gmelin believes that cardiac disorders in non-toxic goiter are due to mechanical pressure effect. Cardiac damage due to direct toxic thyroid effect may be evinced by abnormal function without definite pathologic change. Gmelin believes that the tachycardia is often due to an abnormal susceptibility of the heart to stimuli.

Sulger<sup>7</sup> in an exhaustive experiment in 1927 determined the effects of different types of tracheal compression upon the heart; he found that not all forms of tracheal stenosis cause cardiac dilatation, but that such dilatation is caused only by so-called “even stenosis” (that is, equal hindering of inspiration and expiration) and by so-called “suction breathing” or hindrance to inspiration alone. He further showed that the increased cardiac volume was due primarily to dilatation of the right heart and that the pressure in the pulmonary artery was not much changed in the light forms of stenosis, but might be decreased in more severe grades. Obstruction to expiration alone was found to be least injurious to cardiovascular efficiency. Such conditions, of course, are often encountered under physiologic circumstances such as singing, swallowing, various athletic exercises, etc. Continued obstruction to inspiration soon resulted in cardiac enlargement and increased pressure in a pulmonary artery and veins, and was incompatible with prolonged life. Sulger con-

cedes that his experimental conditions could not be made to conform closely to those obtaining in cases of tracheal pressure from enlarged thyroid because of the factor of adaptability existing in the latter instance. He believes that the main factor producing cardiac dilatation clinically is the increased inflow of blood to the right heart during diastole, and that subsequent cardiac hypertrophy is a consequence of the continued pressure of the larger amount of blood upon the cardiac wall.

Comparatively little attention has been paid to the possible importance of these mechanical factors by American and English writers. Indeed, it seems that while such mechanical agencies might be effective in a comparatively small group of individuals suffering from large goiters with marked tracheal compression, nevertheless such an explanation would apply to only a very small percentage of the total number of patients showing thyroid heart disease of one type or another. It is well known, for instance, that severe cardiac damage may be seen in hyperplastic toxic thyroid disease in which the thyroid is little if any enlarged. It is also true that many patients exhibit marked degrees of tracheal compression over prolonged periods without manifesting signs of cardiovascular damage.

In considering a possible toxic cause it would seem conceivable, although certainly not susceptible of proof, that in certain individuals with thyroid enlargements—but without the usually accepted manifestations of thyroid toxicity, *i. e.*, signs of increased basal metabolism—there may be a toxic agent secreted by the thyroid with a more or less specific degenerative effect upon the cardiovascular apparatus, but without demonstrable effect upon metabolism and without ability to produce those disturbances of the sympathetic nervous system which are so characteristic of certain types of hyperthyroidism. The factor of coincidence should by no means be forgotten, and it must be admitted that in both of the cases here reported the cardiovascular disease and thyroid enlargement may have existed purely coincidentally, as did in all probability the diabetes and thyroid enlargement in the first case; nevertheless, statistical studies such as those of Coller<sup>2</sup> and of Bigler and

Bauer (quoted by Dameshek<sup>8</sup>) demonstrate clearly that cardiovascular disease does occur with increased frequency among patients with various types of non-toxic goiter, whether colloid, parenchymatous, or adenomatous. Since it would appear that the continued existence or growth of a simple goiter is accompanied by a definitely increased incidence of cardiovascular disease in the later decades of life, another cause for indictment may be listed against thyroid enlargements, even though they be not toxic in the ordinarily accepted sense. The therapeutic inference scarcely requires emphasis—the simple goiter in childhood, adolescence, or early adult life should be treated medically and the patient kept under close observation. Persisting or increasing thyroid enlargements in adult life, particularly if firm or nodular in consistency, constitute a potential menace to the cardiovascular system and surgical treatment is advisable.

**Conclusions.**—1. The incidence of cardiovascular disease is greater in patients with so-called simple or non-toxic enlargements of the thyroid than in the average general population, particularly in the later decades of life in goiter belts.

2. The manner in which such cardiovascular damage may be produced is not known.

3. It would seem possible that goiter not capable of producing the syndrome of "hyperthyroidism" in the generally accepted sense of the term might nevertheless produce an agent capable of injuring the myocardium and vascular apparatus.

4. The so-called "mechanical theory" of cardiac damage being indirectly produced by pressure of the thyroid on the trachea, even if correct, could apply to only a small group of those individuals showing evidence of heart disease with simple goiter.

5. A further reason for the energetic treatment of simple goiter is presented and the prophylactic value of surgical removal of persisting thyroid enlargements in adult life is suggested.

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CLINIC OF DRS. BURGESS GORDON AND  
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THE USE OF DEXTROSE AND A MODERATELY LOW  
CALORIC DIET IN THE TREATMENT OF OBESITY,  
WITH SPECIAL REFERENCE TO THE EFFECT IN  
PATIENTS WITH DISTURBED CIRCULATION\*

THE problem of obesity is difficult to solve, perhaps because the mechanism controlling the maintenance of the normal weight is unexplained. The influence of such possible factors as disturbance of the endocrine glands and water metabolism and lowered respiratory quotient has been considered. Although these phenomena are present in certain obese patients and are influenced by treatment, the changes in metabolism are not accompanied regularly by loss of weight.

Since the cause of overweight is not established, the clinical management of obesity depends to a certain extent on empirical forms of treatment. In general the treatment consists of a plan for reducing the total intake of food with or without an increase of exercise or the administration of glandular extracts.

It appears that unsatisfactory results may be due, in part, to the inability of the patient to tolerate a low caloric diet. In certain instances the chief symptoms are fatigue, hunger, nervousness, and weakness. These hypoglycemic-like manifestations lead eventually to the excessive intake of carbohydrate. An hypothesis<sup>1, 2</sup> to explain the occurrence of symptoms and the rationale for treatment is as follows: The excessive intake of starch results in the stimulation and oversecretion of the

\* From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest.

pancreas (Harris<sup>3</sup>), and, eventually, in a general disturbance in the storage and utilization of carbohydrate. The condition is aggravated by exercise, and the symptoms are relieved apparently by the administration of carbohydrate. Since physical inactivity and the excessive intake of food may cause obesity, the possible effect of insulin on the gastro-intestinal tract and tissue cells which according to Fonseca<sup>4</sup> has a favorable influence on emaciation, may be a further important factor in the gain and maintenance of overweight.

The so-called "dextrose moderately low caloric diet" is suggested as a means to assist the patient in comfortably taking exercise, in returning to moderate food consumption, and perhaps in restoring to normal a phase of disturbed carbohydrate metabolism. The régime is as follows: The patient tabulates accurately for three days the occurrence of various symptoms, the extent of exercise, and the amount and type of food consumed (Chart). On the fourth day, if there is no contraindication to a loss of weight, a 1200-1400 caloric diet, consisting of 3 to 5 per cent. vegetables, 2 to 3 pieces of bread and butter, 100 gm. of meat, clear soup, 2 small potatoes, 2 glasses of milk, and 1 orange is prescribed. The patient's activities and symptoms are recorded as usual on the diet symptom chart. On the fifth day the moderately restricted diet is continued, but, in addition, 2 gm. of dextrose in the form of lozenges, candy, or powder are administered every half-hour from 9.30 to 11 A. M.; 2.30 to 5.30 P. M., and 8.30 to 9.30 P. M. (breakfast 7.30 A. M.; luncheon 12.15 P. M.; supper 6.15 P. M.). On the sixth day the starch portion of the total caloric intake is reduced further and the half-hourly dosage of dextrose is increased from 2 to 4 gm. at 10.30 A. M. and 3.00 and 3.30 P. M. or at other times to relieve symptoms of fatigue, hunger, nervousness, or weakness. The patients are urged to walk 1 km. leisurely in the morning or afternoon at the beginning of the diet. The distance should be increased gradually until at the end of two weeks 4 km. are covered daily. The régime is discontinued after one month and a moderately restricted diet (1400 to 1800 calories) is prescribed. If a further loss of weight is desired the diet

Name	Date																																			
Hour <sup>1</sup> .....													P. M.																							
Water <sup>2</sup>																																				
Food <sup>3</sup>	Breakfast (approximately 200 calories)												Luncheon (approximately 500 calories)												Supper (approximately 400 calories)											
Hunger	✓																																			
Weakness	✓																																			
Fatigue																																				
Drowsiness																																				
Nervousness																																				
Perspiration																																				
Strength																																				
Dextrose <sup>3</sup>																																				
Exercise <sup>4</sup>																																				
Weight																																				

NOTES.—<sup>1</sup> List activities and symptoms under hour at which they occur.

<sup>2</sup> Give in detail amount of food and water at each meal and between meals.

<sup>3</sup> Record number of candies.

<sup>4</sup> State exercise in blocks covered.

State impression of the effect of the diet upon general condition.

Hours sleep on previous night.

DIET-SYMPHOM CHART.—A tabulation to show the occurrence of symptoms in an obese individual and the management of the dextrose moderately low caloric diet. In addition to the routine administration of dextrose four lozenges were prescribed at 10 and 10.30 A. M. when symptoms of hunger and weakness occurred. Between 3 and 4 P. M. four dextrose lozenges were administered in anticipation of symptoms noted on the previous day. This patient had consumed cake and bread and macaroni in large quantities at mealtime and between meals. In the diet these foods were omitted between meals and reduced in quantity (approximately one-third) at mealtime.



is resumed after a rest period of two to three weeks. As the danger of a rapid loss of weight is appreciated, no patient, unless extremely obese, is permitted to lose more than 2 kg. weekly. A physical examination and a study of the urine are made at intervals during the course of treatment. This plan for observing the patient seems advisable because obesity, in a measure, should be regarded as a pathologic state requiring careful supervision. Under no circumstance is the diet continued if untoward effects are noted.

Dextrose was selected for administration because it was considered a readily available fuel and not likely to cause gastric distress when taken in large doses. The candy was manufactured according to the following formula: 1000 gm. of dextrose (Corn Products Refining Company), 250 c.c. of honey, 60 gm. of butter, and 500 c.c. of water are cooked rapidly. When a temperature of 278° F. is reached the cooking is stopped. During the entire cooking the sugar is stirred vigorously. The mixture is then poured on a marble slab, flavored (peppermint, lime, raspberry, orange, vanilla, and chocolate obtained from cocoa shells), and then made into taffy in the usual manner. The candy is rolled and cut into pieces weighing 4 gm. (each candy contains about 2 gm. dextrose) and wrapped in waxed paper. Dextrose lozenges weighing 2 gm. were made by simple compression, no ingredients being used other than flavoring extracts (peppermint, wintergreen, or lemon). Dextrose powder dissolved in orange juice or lemonade has been acceptable to several patients. Different flavors of dextrose candy, powdered dextrose, and lozenges have been prescribed on alternate days so as to provide variety in the diet. It appears that lozenges are the most satisfactory means for the administration of divided doses of dextrose. They are easily manufactured and are not distasteful to the patients.

The diet has been used in 92 patients with so-called exogenous type of obesity. In 46 instances the average loss of weight was 1.5 kg. weekly. The greatest loss occurred usually during the first week (1.5 to 3.5 kg.). In 29 patients considerable fluctuation has been present, such as a loss of 2 kg. during the first

week, a maintenance or gain of about 0.5 kg. during the second week, and a further loss of one or more kg. during the third or fourth weeks. During a period of ten to fourteen days when dextrose administration was discontinued and the patients followed a less restricted diet, it was rare for a gain of more than 0.5 to 1 kg. to occur. Forty-seven patients have been under observation for over fourteen months. The greatest loss has been 49 kg., the average being 11 kg. Fourteen patients have been on a moderately restricted diet four months after discontinuing the dextrose régime. The average loss maintained was 5.5 kg. So far as determined there have been no ill-effects other than transient headaches in a few patients at the beginning of the diet and constipation and a sensation of fulness in the stomach if the intake of dextrose was excessive. It is noteworthy that the régime has caused no mental depression and that gastric distress previously noted has been relieved. In many instances the craving for starch has disappeared. The failures have been due apparently to the possible influence of endocrine disorders and the lack of co-operation of the patients.

In a small group of ambulatory obese patients with disturbed circulation a rather striking general improvement was noted. A reduction of blood-pressure and relief from dizziness and shortness of breath were definite in 8 patients. In 2 patients with edema marked diuresis occurred. In studying the occurrence of symptoms it appears that obese patients require the timely administration of carbohydrate. This may account for the abnormal intake of bread, cake, rich desserts, candy, and beverages. In the dextrose moderately low caloric diet an attempt is made to assist the patient in cultivating normal habits of food consumption. The chief points of the diet are the reduction in the intake of carbohydrate (approximately one-third of the former amount consumed at mealtime) and the administration of dextrose in divided doses between meals. Although certain types of food may be suggested, it is usually unnecessary and often unwise to change the varieties which appeal to the patient; as, for instance, the patient may enjoy a breakfast comprised of fruit, three slices of toast, one bowl of

oatmeal, cream, potatoes, bacon, eggs, and coffee. On diet one slice of bread, a portion of one potato, and two or three tablespoonfuls of oatmeal would be allowed. No change is made in the amount of bacon, eggs, and coffee. Since dextrose is administered between meals there would be no considerable reduction in the total number of calories as compared with the intake before the diet was instituted.

Obviously the hypothesis suggesting that obesity is due to the excessive intake of carbohydrate and oversecretion of the pancreas is speculative. It is unproved, also, that a restriction of the customary intake of carbohydrate and the administration of divided doses of dextrose reduces the stimulation of the pancreas. However, it is likely that dextrose provides readily available fuel, adds to the storage of glycogen, and exerts a specific dynamic action. Weight may be lost because the caloric intake at mealtime is insufficient for maintenance of excessive fat.

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## CLINIC OF DR. RUSSELL RICHARDSON

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#### URINE EXAMINATIONS IN DIABETES MELLITUS

BEFORE the advent of insulin the changes in blood and urine sugar in diabetes, brought about by changes in diet, were so gradual that twenty-four-hour urine specimens were sufficient with an occasional blood-sugar to indicate the result of a given diet. On the other hand, since we have had the use of insulin we have been able to bring about marked changes in blood and urine sugar in a few hours. It has been found desirable to use, with the twenty-four-hour specimen, something that would give us information sooner and more definitely regarding the results of the individual doses of insulin. If we attempt to get this information from ambulatory patients by means of blood-sugars, we are met by the practical difficulties of obtaining so many specimens of blood, as well as by the objections of the patient. If we find a normal renal threshold for sugar, urine specimens may be satisfactorily used.

To obviate these difficulties we have been using for some time at the Metabolic Clinic of the University Hospital urine specimens collected at stated times during the twenty-four hours. The times which we have chosen for these specimens are at 11 A. M., 4 P. M., and 9 P. M. on the day before the visit to the clinic and before the morning insulin on the day of the clinic visit. These can be collected as single specimens at the times mentioned or as portions of a twenty-four-hour specimen, each one containing all of the urine voided since the preceding time. In the clinic we have used the former, as our patients are not able, on account of their work, to make the more elaborate collections. The patients bring to the clinic four small vials

containing portions of these specimens. These specimens are examined, using 8 drops of urine and 5 c.c. of Benedict's solution, and the results recorded as 0 (clear blue or blue green), + (thick green color, less than 1 per cent.), ++ (yellow green, approximating 1 per cent.), and +++ (yellow, approximating 2 per cent.). We reserve ++++ for all specimens above this amount as shown by a very rapid change after slight boiling.

The daily régime is then noted as follows and our treatment guided accordingly:

Insulin—units  
Breakfast C/P/F  
Urine specimen at 11 A. M.  
Insulin (if given)  
Lunch C/P/F  
Urine specimen at 4 P. M.  
Insulin (if given)  
Supper C/P/F  
Urine specimen at 9 P. M.  
Urine specimen before insulin the following morning

Each portion of the day may be studied as a unit, taking into consideration the insulin, the succeeding meal, and the urine specimens voided before and after them, as follows: Urine specimen (sugar), insulin in units, meal C/P/F and urine specimen after the meal. If the urine sugar is greater in amount after than before the insulin and meal, then we know that the insulin has been too small or the meal too large and we alter them accordingly. This can be repeated for each meal and the supper can be studied as regards its affect on the night and morning urines. As the days are apt to be very similar, if the insulin and diet are fairly well adhered to, we can use the early morning specimen as representing the beginning of both days.

Table I shows a few possible combinations.

In Number 1 we find the day starts satisfactorily, but that the morning insulin is too small for the breakfast, as is also the evening insulin for the supper. An increase in insulin or reduction in diet is the only remedy. In Number 2 we find that while 10 units will do for the breakfast and lunch, 7 units will not do for supper. Here we may either increase the

TABLE I

	1	2	3	4	5	6	7
Urine sugar.....	0	0	0	+++	+++	0	0
Insulin units.....	10	10	10	20	20	10	15
Breakfast C/P/F.....							
Urine sugar.....	++	0	0	0	+	++ shock	0
Insulin units.....	0	0	0	0	0	0	0
Lunch C/P/F.....							
Urine sugar.....	+	0	++	0	+ shock	0	+
Insulin units.....	7	7	7	7	7	7	7
Supper C/P/F.....							
Urine sugar.....	+++	++	++	+++	+	0	+

insulin, reduce the supper, or transfer some of the supper carbohydrate to one of the other meals which seem to be well taken care of. In Number 3 the morning dose is satisfactory for the breakfast, but does not give sufficient insulin to carry also the lunch; so of course it must be increased so that it will last through the day, until the evening dose is given. The 7 units will then continue the patient sugar free after supper. The start of the day in Number 4 is not good, due to the amount of sugar present remaining over from the supper of the preceding evening. The 20 units of insulin is large enough for the breakfast, in fact too large, for if we will increase the evening insulin and thus begin the day sugar free, we could use a much smaller amount of insulin in the morning dose. Number 5 presents a similar problem except that here there is only a small amount of sugar present in the evening and a large amount the following morning. The patient cannot take care of even the physiologic sugar of the postabsorptive state. If we greatly increase the evening dose of insulin we would cause shock during the night before we would be able to make the morning urine sugar free. Our only course here is to increase the evening dose slightly, to get our patient sugar free during the early part of the night, and then either give a midnight dose of insulin or accept the fact that our patient will have sugar for a few hours in the early morning. We find in Number 6 an example of giving the insulin too near breakfast. The breakfast is absorbed faster than the insulin and increases the blood-sugar to the extent of spilling over into the urine. The insulin absorbed later, when there is

not sufficient sugar in the blood, gives the patient shock in the afternoon. Giving the insulin a somewhat longer time before breakfast will cause its absorption at the same time as that of the meal, thus removing the sugar at 11 A. M., and because the insulin has been used on this sugar, removing the afternoon shock. In Number 7 we have a combination in which moving a few grams of carbohydrate from lunch to breakfast will remove the shock in the morning and the sugar after lunch, and perhaps allow the evening insulin, working on a lower blood-sugar, to take care of the supper sufficiently to remove the evening sugar.

All these and many more have occurred in the routine care of our patients. These, however, suffice to show the possibilities to be realized if we study carefully these four specimens in relation to the insulin and meals. They may not cover the entire time, but within their limits they seem to point more definitely to the changes which we can make in the care of the patients. Of course occasional blood-sugars should always be used as a check on the renal threshold.

## CLINIC OF DR. LEON H. COLLINS, JR.

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#### THE PREVALENT PATHOLOGY OF TODAY AS SEEN IN A MEDICAL CLINIC DURING THE PERIOD OF ONE YEAR

TODAY'S literature, both general and medical, is replete with statistical studies. These studies cover almost every branch of the system diseases as well as the general morbidity of the entire population and its associated economic consequences. From time to time the larger insurance companies publish elaborate tables showing the disorders that produce the greatest morbidity and death in the entire United States. Undoubtedly, this work is a great and useful factor in helping to bring before the mind of the general public the subject of preventive medicine and, furthermore, with what the subject of preventive medicine will have to deal during the next generation.

A survey of the mortality statistics of any metropolitan area of today reveals that the infections, such as typhoid fever or tuberculosis, are much further from the head of the mortality list than they were thirty or forty years ago. On the other hand, it would seem that the degenerative disorders and the so-called "diseases of middle age" are steadily increasing in importance. Indeed, this middle-age group has already attracted so much public and philanthropic attention that special foundations are now confining their activities to the preventive and therapeutic problems of the middle decades of life.

Upon analyzing any such group of statistics, it becomes evident at once that the greatest good to be gotten therefrom is an aid in predicting the medical future. Pneumonia is no longer the "captain of the men of death" as it was only a few



generations gone by. Other diseases and disorders are coming to hold this unenviable position. Pre-eminent in this latter group are disorders of the cardiovascular system. The clinical teaching, started some years ago with the phrase "a man is as old as his arteries," is continued and developed today in the nation-wide systematic attack on the rheumatic, the luetic, and the arteriosclerotic forms of cardiovascular disease. From many quarters one gets the impression that circulatory disease is becoming increasingly the *bête noir* of medicine. The usual explanation offered is that it is due to our national habits of life.

On all sides—in medical practice, in medical teaching, and in medical research—essentially the same question arises—Whither are we headed? The primary justification for the existence of the medical profession would seem to be its utility. When we attempt statistical analysis in clinical medicine we are warned by experts to be wary of the conclusions to be drawn because of the innumerable variable factors, human and otherwise, that are beyond our control. They warn particularly about the conclusions that may be drawn from a small series of cases. Nevertheless, realizing its shortcomings, an analysis has been made of the deaths occurring during the period of one year on the Medical Division of the Hospital of the University of Pennsylvania. These cases were all on the service of Dr. Alfred Stengel. For the most part, these patients had been admitted to the hospital from referring physicians. Consequently, a relatively large percentage of them were particularly "interesting cases" where too often our ardor for pathology was dampened by our failure in therapeutics. This feeling of therapeutic ineffectuality was somewhat mitigated in those cases in which we received permission for an autopsy.

Perhaps at this point a few words concerning our autopsy experience would be in order. Our experience has been the experience of others, namely, that we felt the service was running at its best when our autopsy percentage was the highest, and it would be trite here to emphasize again the dependence of clinical medicine on pathology. As has already been stated, a large percentage of our cases are referred to us by physicians

outside the city. These cases often come a long distance. In addition, a considerable proportion of our cases are Jewish, and in such cases that ended fatally we were in most cases unable to get permission for an autopsy. Other clinics have reported better results than ours in this respect, but to date our experience has been very discouraging. The cases coming from a distance and the Jewish cases were the instances where we had the most difficulty. Perhaps in the future, with a better understanding that the autopsy is a constructive and not a destructive thing, our results will be improved in this latter group.

From September 1, 1927 to September 1, 1928, ninety (90) deaths occurred on the Medical Division. In fifty-four (54) of these cases we were able to get permission for an autopsy. These cases have been listed according to the outstanding clinical, laboratory, and pathologic findings. They are shown in the following table:

RÉSUMÉ OF DEATHS ON MEDICAL DIVISION, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, SEPTEMBER 1, 1927 TO SEPTEMBER 1, 1928.

Total deaths.....	90
Total autopsies.....	54
Autopsy percentage.....	60

PATHOLOGY

Cardiac disease (myocardial and valvular).....	15
Cardiorenal disease.....	11
Cerebral hemorrhage.....	10
Lobar pneumonia.....	8
Bronchopneumonia.....	4
Meningitis.....	4
Anemia.....	3
Bronchiectasis.....	3
Diabetes.....	2
Lymphosarcoma.....	2
Miliary tuberculosis.....	2
Primary carcinoma of the liver.....	2
Acute yellow atrophy of liver.....	1
Amyotrophic lateral sclerosis.....	1
Asthma.....	1
Appendiceal abscess with secondary generalized peritonitis.....	1
Carcinoma of colon.....	1
Carcinoma of esophagus.....	1
Carcinoma of ovary with metastasis.....	1

Carcinoma of body of pancreas with metastasis.....	1
Carcinoma of peritoneum(?) .....	1
Carcinoma of stomach.....	1
Carcinoma of tongue.....	1
Cirrhosis (biliary) of liver.....	1
Colitis (multiple secondary liver abscess—amebic).....	1
Gliomatous cyst with hemorrhage.....	1
Hemachromatosis.....	1
Hodgkin's disease.....	1
Leukosarcoma.....	1
Lymphatic leukemia.....	1
Myelogenous leukemia.....	1
Pick's disease(?) .....	1
Septicemia (streptococcic).....	1
Subacute infective bacterial endocarditis.....	1
Tetanus(?) .....	1
Thyrotoxicosis.....	1
Total.....	90

This summary of our experience over the period of one year shows the following salient features from the standpoint of causation of death:

	Deaths.	Percentage of total deaths.
Diseases of the circulatory system .....	30	33
Pneumonia (broncho- and lobar) .....	12	13
Malignancy .....	12	13

In conclusion, an analysis of this small series of cases shows essentially the same thing that much more elaborate studies have shown from the country as a whole, namely, that in the adult population disease of the circulatory system is the outstanding cause of death and, further, that pneumonia and malignancy follow next, but with a considerably lower percentage.

